PROPOSAL TO WITHDRAW APPROVAL FOR THE BREAST CANCER INDICATION FOR BEVACIZUMAB (AVASTIN)

FDA PUBLIC HEARING

TUESDAY, JUNE 28, 2011

8:00 a.m. to 3:30 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

MEETING ROSTER

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

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INDUSTRY REPRESENTATIVE (Non-Voting)

Gregory Curt, M.D.
U.S. Medical Science Lead, Emerging Products
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TEMPORARY VOTING MEMBER

Natalie Compagni-Portis, Psy.D.

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C O N T E N T S

P R O C E E D I N G S

(8:01 a.m.)

Opening Statement by Presiding Officer

DR. MIDTHUN: Good morning. Can everyone hear me?

Good morning and welcome to this hearing. I am Dr. Karen Midthun, the director of the Center for Biologics Evaluation and Research. However, this morning, I am acting in the capacity as presiding officer in this hearing. I am doing so at the request of Commissioner Margaret Hamburg. Based on the record created, Dr. Hamburg will make the final decision on the issues presented at this hearing. She will take into account what transpires at this hearing and the submissions to the public docket. Dr. Hamburg asked me to convey how seriously she takes this hearing and the need for the science to be presented and examined in an open, systematic and thoughtful manner.

As we begin this hearing, I also want to underscore that FDA understands the enormous challenges we face with respect to breast cancer,

especially metastatic breast cancer, and how hard it is for patients and the families trying to cope with this devastating disease and the need for more effective treatments. I will begin by discussing what is at issue in this hearing and then describe the procedures we will follow today and tomorrow.

At the outset, I want to make clear that this hearing has a very specific focus and structure. This hearing is about Avastin's indication for use in combination with paclitaxel for the treatment of patients who have not had chemotherapy for metastatic HER2 negative breast cancer. Avastin is also an approved treatment for advanced colon, lung, kidney and brain cancers. Avastin's approval with respect to these cancers is not a topic at this hearing.

The approval of Avastin for the treatment of metastatic breast cancer was pursuant to FDA's authority to approve certain drugs under an accelerated procedure. This procedure is available when FDA concludes there is some evidence the drug will provide a clinical benefit that justifies its

risk, but there is not sufficient evidence to support a traditional approval. This kind of accelerated approval is subject to a requirement that the applicant must perform additional, well-controlled clinical investigations to verify and describe the expected clinical benefit.

Here, the applicant, Genentech, completed two additional clinical trials, which you will hear referred to as AVADO and RIBBON 1. The Center for Drug Evaluation and Research, which is responsible for the approval of this drug, ultimately concluded that the results of these additional studies did not justify continued approval. Therefore, the Center notified Genentech it was proposing to withdraw approval of this indication for the drug.

Genentech did not agree with the Center's evaluation of the data, and following the procedures set out in FDA regulations, requested a hearing on the Center's proposal to withdraw the approval. When a hearing is granted on a proposal to withdraw an accelerated approval, the center proposing to withdraw the approval and the

applicant become parties to a hearing.

Representatives of the two parties, the Center for Drug Evaluation and Research and Genentech, are sitting at the front of the room with the Center to my left and Genentech to my right. Also in attendance at this hearing are members of the oncologic drugs advisory committee, and they're sitting immediately to my left. They will consider the evidence presented at this hearing and will tomorrow afternoon provide their advice and recommendation for the Commissioner's consideration.

As I noted earlier, Dr. Hamburg, the Commissioner of Food and Drugs, will make the final decision on whether or not to withdraw the approval of Avastin for the metastatic breast cancer indication. Her decision will be based on the record compiled during the hearing, which includes the information presented here today as well as information submitted to the docket.

The public docket has been open for many months, since the time when the Center announced

its initial proposal to withdraw approval last December, and many people and organizations have submitted comments. In addition, all the submissions by the parties, including the scientific studies upon which they rely, are included in the public docket. The docket will continue to remain open until July 28th of this year at which point it will close.

Where we had earlier stated the docket would close on July 14, Genentech and the Center have jointly requested an opportunity to have until July 28th to submit their final summaries for their respective views on these issues, and I have granted that request and have decided that in light of that request, we will keep the docket open for every submission until July 28th.

There are four issues to be addressed in this hearing, and those issues are dictated by the statute and regulations relating to accelerated approval. The issues which were set out in the Notice of Hearing are as follows:

1, do the AVADO and RIBBON 1 trials' failure

to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved;

2(a), does the available evidence on Avastin demonstrate that the drug has not been shown to be effective for the breast cancer indication for which it was approved;

2(b), does the available evidence on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication for which it was approved and that Avastin has not been shown to present a clinical benefit that justifies the risks associated with use of the product for this indication;

3, if the Commissioner agrees with the grounds for withdrawal set out in Issue 1, Issue 2(a) or Issue 2(b), should FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit?

This morning, our hearing will begin with an opportunity for pre-registered members of the

public to provide their views. Thirty-five people have signed up to make public presentations, and we've divided the time equally so they have up to three minutes each. To help us keep on schedule and ensure all who have signed up to speak have the opportunity to do so, we have a light system that will go from green to yellow when there is one minute left and then to red to let the speaker know their time has come to an end. We will all listen with interest to the presentations, but there will not be any questions asked of the presenters.

After the public presentations this morning, which will take about two hours, we will take a short break and then move on to the presentations by the two parties.

This is how we will proceed. First, presenters from the Center for Drug Evaluation and Research will explain the Center's reasons for the proposed withdrawal. The presenters will take turns speaking from the lectern, over there, and then will sit at the tables to my right, over there. They will have two hours to make their

presentations. That should take us to about 12:30, and we will have a one-hour period for lunch.

There will then be a one-hour opportunity for representatives of Genentech to ask questions of the Center presenters. After that, there will be a one-hour opportunity for me and for members of the advisory committee to ask questions of the Center presenters. There will then be a 15-minute opportunity for Center representatives to ask the Center presenters any clarifying questions. After that, we will break for the day.

Tomorrow, we will start with a two-hour opportunity for Genentech to present the reasons it believes the approval should be continued. After a short break, Center representatives will have a one-hour opportunity to ask questions of the Genentech presenters. There will then be a one-hour opportunity for me and the members of the advisory committee to ask questions of the Genentech presenters followed by a 15-minute opportunity for Genentech representatives to ask the Genentech presenters any clarifying questions.

We will then break for lunch.

After lunch tomorrow, there will be an opportunity for members of the advisory committee to discuss the issues presented. This will be a public discussion, but only advisory committee members and I will participate in that discussion. The discussion will be followed by a vote by the advisory committee members on their recommendations with respect to the four issues presented. All of the members of the committee, except for the member whose role is to represent the views of industry, may vote.

The vote of the advisory committee will not, of course, decide the issues. Instead, Commissioner Hamburg will consider the advisory committee's recommendations along with the rest of the record as she makes the final decision.

At the end of the day tomorrow, I will have a few closing remarks, and that will end the oral part of the hearing. Everyone will then have until July 28th to submit anything they wish to submit in writing to the hearing docket.

One recent development requires a further explanation to the advisory committee members and to the public. On June 23rd, 2011, counsel for Genentech provided counsel for the Center notice that it may address at the hearing updated safety data for the National Surgical Adjuvant Breast and Bowel Project C08 trial of Avastin's effect in combination with N-FOLFOX 6 in early stage colon cancer that had recently become available to it.

Given that the information was submitted very close in time to the hearing, I recognize that the Center may not have had sufficient time to review the information and may not be prepared to address it in the oral portion of this hearing. If Genentech does address these data in the hearing, the Center may provide comments regarding this information in its post-hearing submission to a docket by July 28th.

The next step in the hearing will be for Dr. Michael Ortwerth, director of the Advisory Committee Oversight and Management staff in the FDA's Office of Special Medical Programs, to read a

short statement concerning the conflict of interest clearance of the advisory committee members. After that statement, we will move to presentations by members of the public.

Dr. Ortwerth.

DR. ORTWERTH: Good morning. Thank you.

With the exception of the industry representative, all members of the committee are special government employees and are subject to federal conflict of interest laws and regulations. The following information on the status of the committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found in 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, the FD&C Act, is being provided to participants in today's hearing and to the public.

FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular

federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise. Related to the discussion of today's hearing, members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants or CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Based on the agenda for today's hearing and all financial interests reported to the committee

members, no conflict of interest waivers have been issued in connection with this hearing.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Gregory Curt is participating in this hearing as a nonvoting industry representative acting on behalf of regulated industry. Dr. Curt's role in this hearing is to represent industry in general and not any particular company. Dr. Curt is employed by AstraZeneca.

We would like to remind members that if the discussion involves any other product or firm not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement, and their exclusion will be noted for the record.

We ask that the advisory committee members take care that their conversation about the topic at hand take place at the open forum public hearing. The committee is reminded to refrain from discussing the hearing topic during breaks or lunch

or between the end of today's session and the start of tomorrow's. Thank you very much.

Presentation by Non-Parties

DR. MIDTHUN: Thank you.

We will now move on to the next portion of our hearing. For the next two hours, we will be receiving comments from persons other than the parties. FDA places great importance on public participation in this process. The insights and comments provided can help the agency and this committee in the consideration of the issues before them.

For those planning to speak during these two hours, I thank you for taking the time to participate in this hearing today. You as well as other members of the public also may submit comments to the docket. One of our goals today is to listen carefully to our participants so that those who have signed up to speak have the opportunity to do so. I will call on you in numerical order, and we will be using a lighting system. The light will turn yellow when you have

one minute left and will turn red when the allotted time is over. I thank you for respecting that, and I will now ask the first speaker, Lisa Schlager, to come to the microphone.

MS. SCHLAGER: Good morning. Facing Our Risk of Cancer Empowered represents about three-quarters of a million people living with a BRCA mutation or hereditary cancer risk. Our community includes women with advanced breast and ovarian cancer, many of whom have benefited from Avastin. We are strongly opposed to the FDA removal of the metastatic breast cancer label from the indications for Avastin.

This change will halt access for newly-diagnosed women with metastatic cancer who may benefit from this therapy. Likewise, insurance companies may use the FDA decision to restrict reimbursement for those currently benefitting and responding to the drug.

Research shows that certain women with metastatic breast cancer benefit from the drug. Although we do not yet know who benefits most, we

know that BRCA-associated cancers respond to certain treatments differently than sporadic cancers, and there is anecdotal evidence to suggest that BRCA mutation patients may be among those that respond well.

FORCE conducted a pilot survey among our metastatic cancer patients. The numbers have not been fully analyzed, but we're working with the researchers at Moffitt Cancer Center to review the data more completely. We asked these women whether they had ever taken a therapeutic agent for their metastatic cancer and whether their oncologists felt that their cancer responded.

Among the women who indicated that they received Avastin, all reported a positive response. Nearly half of those who had taken the drug said their cancer responded and has not progressed. The number with no progression was greater for Avastin than other agents approved for metastatic breast cancer, including capecitabine. While our survey is preliminary, it suggests that the hereditary cancer community responds well to the drug.

Those with a BRCA mutation or hereditary breast cancer already face significant burdens. Our cancers are earlier in onset, more aggressive, and often strike multiple family members. We implore the FDA not to limit the treatment options for our community.

I'd like to read a quote from one of our members. "Nearly three and a half years ago, I was diagnosed with Stage 4 breast cancer with mets on my liver. After being advised of the potential side effects, I chose to enroll in a clinical trial which included Avastin. I was able to measure the tumor in my breast with a ruler and watch it shrink before my eyes. PET scans revealed the same result in my liver, along with descending tumor markers. After six months, a PET scan revealed no evidence of disease. All of my scans since then have shown the same result. Nearly three years without evidence of disease.

"This is why I am asking that Avastin stay available for metastatic breast cancer patients. After diagnosis, I learned that I have a BRCA2

mutation. Is it possible that Avastin works particularly well in those with BRCA mutations? I am living, breathing proof that Avastin works for some people. Continued access is critical. FORCE agrees that further research is needed, but we need to move beyond one size fits all cancer treatment."

[Applause.]

DR. MIDTHUN: Thank you.

Will the next speaker please come to the podium, Steve Walker?

MR. WALKER: My name is Steve Walker. I'm cofounder of the Abigail Alliance for Better Access to Developmental Drugs, a nonprofit, nonpartisan patient advocacy organization dedicated to assisting people with serious and life-threatening diseases and unmet needs. I'm an unpaid volunteer. I pay my own expenses, and I have no financial conflicts regarding this hearing.

The Abigail Alliance strongly opposes the FDA's decision to rescind the accelerated approval of Avastin for the first-line treatment of metastatic breast cancer. Based on our

comprehensive knowledge of the law, regulations and the science at hand, we agree with the sponsors that Avastin continues to meet the standard for accelerated approval and should retain that approval.

I'd also like to note that this hearing is taking place within a procedurally corrupt administrative process. Dr. Pazdur selects all the appointed ODAC members from the nominations submitted for those posts. He also decides when temporary voting consultants will be added to an ODAC meeting and directly selects them, no nominations or prescreening required.

Dr. Pazdur's control of this ODAC is relevant to this hearing. Much of the record leading us to this hearing consists of discussions and votes on the prior ODAC meetings regarding this indication, and the panel hearing this appeal consists of a subset of current ODAC members.

Five members of the current ODAC roster are present today. Dr. Balis was selected for ODAC by Dr. Pazdur after this hearing was requested by

Roche Genentech and scheduled by the FDA. The rest were selected for ODAC by Dr. Pazdur before the hearing was scheduled.

These facts were confirmed to me by Jayne Peterson, deputy director of the CDER advisory committee office, and Dr. Michael Ortwerth, director of the advisory committee staff in the FDA's commissioner's office in a teleconference last Thursday.

With the exception of Dr. Balis who is new and Dr. Curt, who isn't allowed to vote, they all voted to rescind approval in the July 2010 ODAC meeting. Ms. Portis, the patient representative, attended both prior ODAC meetings and voted against the indication both times.

None of the voting physicians on the panel appear to be engaged in treating breast cancer as a significant part of their clinical research or medical practice. And we have recently learned that CDER has at least partial control of which patient representative is selected for this specific meeting. I asked again this morning about

that, and I still don't have a clear answer. They're saying no for the Avastin hearing, so I'll take them at their word.

In March, Genentech raised serious and well-founded concerns with FDA regarding the biased nature of the ODAC. FDA dismissed those concerns stating that CDER vigorously protects the independence and balance of federal advisory committees. The Abigail Alliance strongly disagrees with FDA on this point. Dr. Pazdur's complete control of ODAC allows him to preordain the advice and opinions he receives from his committee, neutralizing the FDA's decision to observe separation of functions in this case and rendering this hearing essentially a sham.

To our panel here today, the patient community is going to hold everyone involved in this hearing accountable for bringing personal and professional integrity to this process. Given the circumstances, we think you should consider whether recusing yourself is the only way to do that. It's too late to do anything else.

I will have copies of this complete with footnotes documenting everything I said. There are about 300 of them out on the table out there, and you're welcome to take one. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would the next speaker please come to the podium, Patricia Howard.

MS. HOWARD: Good morning. My name is Pat Howard, a metastatic breast cancer patient who since participating in a 2007 New York City clinical trial of Avastin owes her life to Avastin. Although I'm not affiliated with Genentech or any other particular group, I thank you for giving me the opportunity to speak with you today.

At the last meeting on Avastin July 20th, 2010, I, representing thousands of women taking Avastin, was the only patient who spoke before you. At that time, I mentioned that Avastin has given me a super quality of life to enjoy the birth of two grandchildren. I'm here today telling you that another grandchild was born since we first met.

During that meeting, you said that Avastin only takes its patients to first base but that you were looking for a home run. According to the data presented by you at that meeting, I should have been dead years before. I'm still here and happy to tell you that I'm still in the game, eager and willing to take a base at a time until I reach home plate.

It was apparent from that meeting on Avastin, although approved by you for use in treating other cancers, that it was not your drug of choice for metastatic breast cancer treatment. Please hear me. It is mine. Attesting to the fact that I am alive due to Avastin, I can only hope and pray that you continue to offer me that choice. I'm not just a piece of anecdotal evidence. I'm a wife, mother, sister, aunt and grammy and a friend and a vibrant human being worthy of the dignity of being treated as such. I'm not just a statistic. It's in your hands to ensure that I don't become one.

For some inexplicable reason, Avastin works

successfully in some women such as me, women who are labeled super responders. Due to Avastin, I'm experiencing a quality of life that is nothing short of miraculous. Both I and my doctors have complete faith in the drug. As with all medications, there are side effects to Avastin. However, my doctors have been able to keep those side effects at bay while continuing my treatment.

Yesterday, I was in New York City to undergo yet another scan. The result was beyond belief. According to my doctors, there was no evidence of the disease. To be honest, I walk a tightrope from scan to scan, but I'm happy to be able to perform in life's arena. I have the utmost confidence that I'll be able to continue to perform with the help of Avastin.

I ask you that today, that you please hear me plea to continue to be that wife, mother, sister, aunt, friend and grammy for many years to come. I never thought in the United States I would have to beg for a drug that is keeping me and many others alive.

Please approve Avastin as a treatment for my disease. What if I was your wife, your mother, your sister, your friend, and what if I was your grammy?

[Applause.]

DR. MIDTHUN: Thank you.

Will the next speaker, Nancy Haunty, please come to the microphone?

MS. HAUNTY: Good morning. My name is Nancy Haunty. I'm from Seattle, Washington. I'm 41 years old, and I have metastatic breast cancer, diagnosed in September of 2009. I was successfully treated with Avastin given in combination with Abraxane and have been progression-free for 21 months.

I respect that the FDA has an incredibly difficult job balancing the need to maintain high safety and efficacy standards with the desire of patients like me who want access to new and promising treatments. I wish I could provide more than my individual case, as I know there are many variables. However, I hope the committee will

consider individual experiences presented today as we represent the story behind the numbers.

At the time of my diagnosis, I had 14 tumors in my liver, over 30 in my lungs, and two in my spine. I was in excruciating around-the-clock pain. After three months of Avastin and Abraxane, the tumors in my body had decreased in size by nearly 50 percent, the hypermetabolic activity was greatly reduced, and my pain was nearly eliminated. By June of last year, all my tumors were quiet and many had resolved completely.

I tolerated Avastin extremely well with very minimal side effects. I understand and appreciate that academic research typically and appropriately discounts anecdotal evidence. But isn't the scientific evidence merely a collection of individual anecdotes?

The median survival benefit and progression-free disease statistics on Avastin may be disappointing in aggregate, but individual results are dramatic. I am now 21 months from diagnosis, symptom free from my cancer. I work full-time, and

I have excellent quality of life.

In spite of disappointing survival benefit, Avastin has been shown to improve progression-free disease, which from a patient's perspective cannot be understated. In the summer of 2010, I climbed to the summit of Mount Adams, the second highest speak in Washington state. I can't think of a better way to describe progression-free survival than spending four days on a mountain climbing to over 12,000 feet.

I'm heartbroken that Avastin does not work well for all patients as it has for me, but the same argument could be made for other treatments that work well for some but fail others.

Finally, I want to stress that patients are capable of making informed decisions, working closely with their oncologist to weigh the risks and benefits in the context of their individual circumstances. My 76-year-old mother, who was diagnosed with metastatic breast cancer five months before I was, would not choose Avastin, but as a 40-year-old with aggressive and extensive mets,

Avastin was a logical choice.

Like all other treatments I've received over the years, I signed an informed consent prior to receiving Avastin. I understood the risks and potential benefits. Thank you for your time and consideration.

[Applause.]

DR. MIDTHUN: Thank you.

Would the next speaker, Crystal Hanna, please come to the microphone?

MS. HANNA: My name is Crystal Hanna, and I will be celebrating my 36th birthday on July 1st. The pictures on the screen are those of me and my family. I was diagnosed with breast cancer in October 2008. I was a runner and had just completed a half marathon in my hometown of Parkersburg, West Virginia. My son Alex was one year old, and my daughter Riley was 4 years old. I had a very aggressive treatment plan which included surgery followed by six months of chemotherapy and seven weeks of daily radiation. Afterward, my next scan was clean. I went back to working full-time,

and I even started running again. We thought we could put that chapter behind us.

It was devastating in July of 2010 when a routine PET scan revealed that I had multiple tumors in my liver and bones. I was referred to Dr. Jame Abraham at West Virginia University Hospital who has dedicated his career to breast cancer research. He strongly recommended Avastin in combination with Taxol.

My next scan was done three months later at MD Anderson in Houston, Texas. We went there for a second opinion, and it showed significant response to therapy. A team of medical experts agreed that I should stay on Avastin for as long as I show benefit.

It has been nearly one year now with follow-up scans every three months, and there is currently no evidence of active disease. I'm a testament that the drug does work. Thank God for answered prayers. I've personally had no side effects from Avastin over the last year. Because of my results, I've had more quality time with my family which

included seeing my daughter get baptized, taking a vacation to Disney World, attending my brother's wedding, and walking the neighborhood with my parents.

Every moment is important to us. Avastin gives us hope. We are counting on the FDA to make the right decision, one that enables all patients, including those newly diagnosed, to have Avastin as an option. Each patient is unique and responds differently. It is morally and ethically wrong to stop treatment for those benefitting.

If the FDA removes breast cancer indication from the label, my insurance likely won't pay, and I can't afford the drug otherwise. If you were me or I was your loved one, wouldn't you want a specialist recommending treatment and the freedom to choose the best options?

Please have compassion and value my life. I'm not just a statistic. Keep breast cancer on label so that I and others like me can celebrate more birthdays. I pray for a cure. Until then, I pray for effective drugs for those who need them

and for me, that drug is Avastin. Thank you and may God bless all those who face cancer.

[Applause.]

DR. MIDTHUN: Thank you.

Would the next speaker, Priscilla Howard, please come to the microphone?

MS. HOWARD: I am a triple negative metastatic breast cancer patient who has been on Avastin with Xeloda, not paclitaxel, for 32 months with positive results, showing no evidence of the original tumor under my arm and a reduction in my lung tumors. I am progression free, PFS, but not cancer free.

My oncologist chose these drugs, knowing that others, including the carboplatins showed greater toxicity, would not be as effective or appropriate for my triple negative cancer.

Why do I believe Avastin is the key? The trial data clearly showed that Avastin in conjunction with either Xeloda or paclitaxel showed greater PFS than either alone. Although new drugs are being researched, if they even get to market,

they won't be available in time for me to be able to use them.

All drugs have side effects, and I've experienced two of the most prevalent and the most readily controlled, hypertension and proteinuria. With medication, I have no sign of hypertension, except right now --

[Laughter.]

MS. HOWARD: -- and my frequent urine samples sometimes require an adjustment in my cycle of Avastin. The key is constant monitoring in consultation with my doctor.

The day may come when by body rejects these drugs, and I'll accept that. But I can't accept others rejecting it for me. Advocates for withdrawal have a simple choice. Don't prescribe it, don't use it, but don't take it away from me.

Data from the Avastin trials do indicate PFS, impacting life and quality of life. Curiously, others reviewing the same data, including the European counterpart, determined the benefit versus risk was sufficient for approval.

What endpoint then is sufficient for your approval? Months, years? Despite potential side effects from Avastin, metastatic breast cancer has only one, death. Certainly, Avastin can do no worse.

Alarmingly, even though Avastin remains available for other cancers with the same side effects if approval is withdrawn, insurers will stop paying. We can't afford it. While urging your continued approval, I also urge Roche to continue to find ways to make it available and cost effective.

I want every available weapon in my arsenal as I fight this devastating disease. As I face a frightening and uncertain future, I think of the moving poem by Dylan Thomas. I will not go gentle into that good night. I will rage against the dying of the light. And with your help, it will keep burning.

[Applause.]

DR. MIDTHUN: Thank you.

Will the next speaker, Diana Zuckerman, please come to the microphone?

[No response.]

DR. MIDTHUN: Perhaps we'll go on to the next speaker then. If she comes a little later, she can speak them.

The next speaker is Patricia LoRusso.

[No response.]

DR. MIDTHUN: Perhaps if she comes later, she can speak.

The next speaker is Betsy Swersky.

MS. SWERSKY: When I started my breast cancer journey, I never imagined myself speaking before a room full of people. I'm nervous, but just as no one gave me a choice regarding breast cancer, I have no choice but to speak now. My name is Betsy Swersky, and I'm 51. I'm married to my high school sweetheart, and we have three children.

When you are diagnosed with cancer, your world stops while the rest of the world continues to turn without you. Our world came to a halt in December of 2005. There was no family history of cancer, yet I had an aggressive cell type known as triple negative. I underwent a double mastectomy,

a lymph node dissection, chemo, radiation and reconstruction. Finally, after a nightmare year, my hair grew in, I resumed exercising, and I went about my life.

But then a PET scan in October of 2008 showed my cancer was back in the opposite side lymph nodes. I had more surgery, more radiation and more chemo; this time with Avastin. Avastin, the drug that left me with no major side effects, the drug that brought me clean PET scans, scans with no evidence of disease, the path to stable blood counts and a normal life. It's been almost three years, and I am doing well and considered free of disease. This is remarkable with a history of recurrent triple negative breast cancer. Avastin is contributing to keeping the cancer at bay and letting me live normally.

I am pleading with you today to keep my miracle drug Avastin available for all breast cancer patients. At the very least, I implore you to keep Avastin available for those of us who are already seeing its benefits. Please require

insurance coverage for Avastin that is already in use. Also, if my oncologist ever decides to try a different treatment, I need to keep the option open to return to Avastin. Please include a provision for the resumption of coverage in such cases.

I have responded beautifully to Avastin. Each person, each tumor is different, and we should all have the same access to medications. Your doctor should have the ability to choose the best drug for you. Significant numbers of women are super responders to Avastin. Until science advances to the point of being able to predict who will respond like this, doctors need the option of trying this drug in patients who might benefit.

Why is Avastin working for me and other super responders? I can't answer that, but it is working. I am here to enjoy my life, to watch my daughter Alyssa (ph) get her master's in teaching, to watch my daughter Heather enjoy her years in college, to see my son Adam pitch for his varsity baseball team, to be a partner to my husband, to travel, spend time with our families and live. The

passing months are turning into years.

The decision to utilize Avastin should be one that my doctor and I discuss privately. I want you to see that I am a real person in need for continued course of Avastin. Thank you so much for the opportunity to address you today.

[Applause.]

DR. MIDTHUN: Thank you.

Will the next speaker, Elizabeth Cleary, please come to the podium?

MS. CLEARY: Good morning. I'm here as another reminder that Avastin does indeed work for some metastatic breast cancer patients. But I think the most important thing for you to note is that I am actually here.

I'm a triple negative metastatic breast cancer patient who underwent 40 rounds of chemotherapy. My disease was stable on a regimen of carboplatin and Taxotere over a two-plus-year period. Avastin was added in July of '06, and with just over two months of Avastin treatment in September of '06, scans showed no evidence of

disease. I have treated with Avastin since that time with most recent scans showing no evidence of disease.

I'm a working registered nurse, and as such, I am fully aware of the risks involved in Avastin use as well as those treatments I have previously received. I have given my informed consent to be treated with Avastin. I do sometimes worry about the side effects and the long-term damages that can be done, but the bottom line is my cardiologist assists in my medical management along with my oncologist by understanding, monitoring and treating for the drug's effects. My oncologist and I are both fairly certain I wouldn't be here right now if it weren't for Avastin. I would be dead.

So for now, I live with hypertension. It requires two prescription medications to manage. In the past when I was on chemotherapy, I used a combination of eight prescription medications, eight over-the-counter medications, multiple noninterfering supplements and several topical treatments just to tolerate the side effects of

chemotherapy. That difference alone applies directly to my ability to live fully as I have been able to do for the past four and one-half years.

Regardless of the indication, breast, colon, brain or lung cancer, Avastin does hold the same risk for all users. That being said, continued research is of the utmost importance for all indications, but future investigations need to be allowed. We're talking about metastatic disease, not growing eyelashes or having a more satisfying sex life.

They say there's power in knowledge, but knowledge loses its punch without wisdom. My life, the lives of my family, and women with metastatic breast cancer depend and hang our hopes on anything that can help us to live and live as fully functioning as the treatment of any metastatic disease will allow. My choice is Avastin; chemotherapy hurts.

I remember 1991, my 26-year-old cousin lie dying of metastatic breast cancer in a major medical center. She begged her parents and mine to

do something to save her young life. I ask that you not take Avastin away from those of us with metastatic disease because first you must do no harm. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would the next speaker, Robert Berger, please come to the microphone?

DR. BERGER: Good morning. I'm Dr. Robert Berger, a gynecologic oncologist, professor and director of the Women's Cancer Center at Foxchase Cancer Center in Philadelphia. I have served as a principal investigator for Phase 2 and Phase 3 trials of antiangiogenic therapy in patients with ovarian cancer.

I am here today on behalf of the Ovarian Cancer National Alliance, a patient advocacy group representing women and men whose lives have been touched by ovarian cancer. I serve on the scientific and medical advisory board of the alliance.

By way of disclosure, the alliance works

closely with Genentech and Roche, the manufacturers of Avastin, and with other pharmaceutical companies, but although the alliance has received funding from the company in the past, its working relationships in no way influence our position.

I think all of us would agree that clinical trials are intended to be pure scientific experiments which must have valid endpoints. Progression-free survival or PFS is often the most objective and, hence, most valid endpoint in a clinical trial. For example, this is true for frontline Phase 3 trials of metastatic cancers where multiple active regimens have been demonstrated and where relatively long post-progression-free survival times have been noted.

Considering the multitude of therapies stacked up through a disease history, it is becoming more and more difficult to demonstrate that any one active therapy can dramatically improve overall survival in a statistically significant sense. With numerous therapies available in metastatic or recurrent cancers,

isolating a single regimen or agent as the sole variable responsible for improvement in overall survival is difficult if not impossible.

We are in a new age in oncology where multiple active regimens exist for diseases like metastatic breast and ovarian cancer. For example, the NCCN has listed single agent Avastin as a preferred regimen, among others, in the management of recurrent ovarian cancer. However, without agency approval, the ability to prescribe the agent is limited, highly variable and discriminatory.

The alliance is here today because clinical trial data for ovarian cancer are not dissimilar to those with metastatic breast cancer. Three Phase 3 clinical trials, two of them placebo-controlled, have demonstrated significant prolongation of PFS with the incorporation of Avastin in the primary and secondary treatment of advanced ovarian cancer and related malignancies. In some cases, these trials have shown trends for prolongation in overall survival.

In addition, a consensus statement by the

GCIG, a global consortium of cooperative groups, lists PFS as the preferred primary endpoint in frontline ovarian cancer Phase 3 trials, including those involving a maintenance component.

We feel if the agency upholds its decision to disapprove the use of Avastin in the frontline treatment of metastatic breast cancer, this could have a negative impact for women with advanced or recurrent ovarian cancer, and we urge you not to limit access to this clinically important agent. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would the next speaker, Stanley Waintraub, please come to the microphone?

DR. WAINTRUAB: Thank you for letting me speak in favor of the clinical efficacy of Avastin in metastatic breast cancer, based on my extensive use of Avastin since ‘05 at the John Theurer Cancer Center, the fifth largest cancer center in America, where I’m chief of breast cancer, and chief of hematology, and above all, I’m Elizabeth’s doctor.

I hope my words will help you to decide not to withdraw Avastin from its breast cancer indication.

Deborah, 49 years old, diagnosed with early breast cancer in ‘05, got CMF, tamoxifen, relapsed with metastatic liver disease in ‘08, treated with Taxol, Avastin, complete total response, remission.

Elizabeth, whom you just met, 51-year-old nurse, triple negative breast cancer in ‘02, got AC, in ‘04 relapsed with tissue proven lung metastatic disease, got Taxotere carbo, had absolutely no response. In ‘06, she got Avastin with the chemotherapy and paid out of pocket. She’s had a complete response and is on Avastin alone in a complete remission since 2006 despite being triple negative.

Nancy, 38, metastatic breast cancer, bone, liver, treated with hormonal therapy and Taxol, Avastin, complete total response on chemotherapy and Avastin, is off that, is only on Femara. She is five years after diagnosis. I just danced at her son’s bar mitzvah.

Stacy, 39 years old, metastatic triple

negative breast cancer, tremendous pain, liver disease, bone disease, Taxol, Avastin. Her PET scan is now normal.

I believe that Avastin coming off the market would be devastating to my breast cancer patients, especially the triple negative group. This is especially true as the PARP inhibitors do not work in first-line triple negative patients, leaving them with toxic chemotherapy without biologic synergistic agents to fight their dreadful diseases.

You know the efficacy of first-line Avastin from the three randomized trials. You know progression-free survivor is longer. You know the objective response rates are higher, and yet you the FDA have approved other drugs with only progression-free survival without overall survival. You approved Ixempra. You approved Tykerb. Why can’t you leave Avastin on the market?

Indeed, Taxol Avastin is approved in Europe based on E2100. Why should a woman in Europe or 86 other countries be permitted to get Avastin in

metastatic breast cancer but not in the United States? I believe the lives of thousands of women will be compromised, they would actually die, if you withdraw Avastin from the market.

Aside from the easily controllable hypertension and occasional nosebleeds, the patients on Avastin have tolerated extremely well. Look at Elizabeth. Does she look sick?

Certainly, there's nothing different from my breast cancer patient than a colon cancer, lung cancer, brain cancer or kidney cancer patient where you have given full unconditional approval. There is nothing different in my patients' safety profile than the other cancers.

On behalf of my thousands of oncologists who treat breast cancer and their wonderful, caring patients and their loving, caring families, I humbly beg you to allow Avastin to remain on the market and not take it off and remain approved for breast cancer. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would the next speaker please come to the podium, Joseph --

DR. SPARANO: Good morning. My name is Dr. Joseph Sparano, associate chair of the Eastern Cooperative Oncology Group and chair of the ECOG breast committee that led the pivotal E2100 trial that formed independently largely in the U.S. by the NCI-sponsored intergroup. And that was published in the New England Journal of Medicine.

After granting accelerated approval for Avastin in 2008 based on E2100 and concluding the results were robust and clinical benefit meaningful, the agency has reversed its decision after review of data from AVADO and RIBBON 1. Despite the agency's declared position and without additional data from E2100, the agency now states however that the clinical benefit in the E2100 trial was an outlier and that the risks of Avastin outweigh its benefits.

The alternative explanation is that Avastin is effective when used with weekly paclitaxel and less effective when used with other agents, as

accepted by European regulatory authorities. ECOG specifically chose the weekly paclitaxel regimen based on preclinical synergy and the desire to continue therapy until progression to maximize treatment benefit.

Regarding the risk-benefit ratio in E2100, survival was significantly approved by 8 percent at one year, a fact corroborated in a combined analysis, including AVADO and RIBBON 1. This consistent early survival benefit when Avastin is actually given, combined with comparable adverse event in identical treatment associated mortality rates, provides irrefutable evidence of a favorable risk-benefit ratio.

The agency has also now stated that the results of E2100 are questionable and less methodologically rigorous than the other trials and cited several specific deficiencies. There is also no basis whatsoever for these concerns. Regarding data quality, the rates of missing, censored and discrepant data for the independent review was similar in the two arms and level of agreement

similar to other trials used to support approval of other agents.

Regarding potential for random high bias, expert statisticians have concluded that early stopping for efficacy introduces negligible bias, specifically when at least 50 percent of events have occurred, as was the case in E2100. Regarding the open label design, a meta-analysis of 27 studies found excellent agreement in both blinded and open label studies.

ECOG and FDA are federally-funded organizations that are key stakeholders in the enterprise approving that new treatments produce clinical benefit. We applaud the agency for its decision to grant accelerated approval in 2008 which has resulted in Avastin becoming widely used and embraced by both cancer specialists and the patients we serve.

There is absolutely no reason to doubt that wise decision now because of AVADO and RIBBON 1. These studies, in fact, did confirm a biological effect of Avastin but also tell us its clinical

benefit is optimized by using it in combination with weekly paclitaxel as in E2100.

The important question in 2011 is not whether the results of E2100 were true, but rather who benefits from Avastin and does continuing Avastin beyond disease progression provide additional clinical benefit. Thank you for your attention.

[Applause.]

DR. MIDTHUN: Thank you.

Would the next speaker, Shannon Morgan, please come to the microphone?

MS. MORGAN: Hi, I'm Shannon Morgan from Charlotte, North Carolina. My husband Pat and my oncologist Dr. John Powderly are here with me. I was first diagnosed in 1999 with Stage 2 breast cancer. I had a radical mastectomy, chemo, radiation and hormonal therapy. I also had reconstructive surgery. In 2001, it reoccurred, and again, treatments were repeated.

I relapsed a little over three years ago with 4-stage metastasized breast cancer in the

abdomen. I was given 12 to 24 months to live with only Femara as treatment. I was told chemo nor any other drug was an option. I had just been given a death sentence.

That wasn't good enough for me and my husband, so we researched and found a caring, well-known and respected oncologist, Dr. John Powderly of BioOncology Institute. He treated me with a triple chemo cocktail and Avastin. After my last round of chemo, I have continued to be treated with Avastin as maintenance.

I am a super responder. I have virtually no side effects. I have a runny nose, and the protein in my urine rises about twice a year. I drink more water, and it drops. He continues to monitor my cancer and feels like Avastin is the proper treatment for me. My recent bone and body scan show that I remain to be in remission almost three years later because of Avastin. Avastin alone is working for me as well as thousands of other women. Avastin alone is keeping our fourth stage breast cancer in remission.

I feel my treatment should be decided between me and Dr. Powderly, not by a panel who does not see me on a regular basis and does not know my medical history.

I work full-time, and up until their recent deaths, I took care of my elderly parents. Avastin has actually given me my life back. It's given my strength, dignity and a positive outlook for life. It's even given me times when I don't think about having cancer.

My insurance company, like most, will probably deny my claims because this drug will not be approved by the FDA. You may be rich, but I am not. If you take Avastin off the label for 4-stage breast cancer, when are you going to take the other cancers off? The side effects appear to be worse for those.

With 4-stage breast cancer, everyone dies, but we hope and we wait for new drugs. Avastin is the only drug that works to block the blood supply. If you take Avastin off label, even to do more research, how many of us successful users do you

think will die during that time? Do you want that on your conscience? If you take Avastin off label, you will be taking my hope and giving me another death sentence.

Please, please, somehow, someway keep Avastin on label for metastasized breast cancer. Avastin is my miracle drug. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would John Powderly please come to the microphone?

DR. POWDERLY: Good morning. My name is Dr. John Powderly. I'm a board certified medical oncologist in Charlotte, North Carolina.

I'm attending at the request of Shannon, one of my patients, and her husband Pat who will speak after me. I'm here as an oncologist and as an investigator for the RIBBON trial and on multiple other antiangiogenesis trials. I'm in full-time private practice, five days a week. I have treated hundreds of breast cancer patients over the past 10 years.

As an oncologist, I have seen multiple Avastin super responders whose initial response to chemotherapy has remained durable, much longer than otherwise would be expected. I am convinced that patients like Shannon who are clearly benefitting from Avastin would have progressed sooner if Avastin was stopped.

Terminal cancer patients are considered vulnerable, and their effective cancer drugs are a huge, unmet medical need. So any, any magnitude of progression-free survival, whether it's from one month or 5.5 months as in the E2100 trial, are significant and should be considered valuable and meaningful clinical benefit. These patients want small but modest increments, if they're available and if it improves their quality of life because they have few alternatives other than more chemotherapy and more radiation.

CDER had commented that Avastin, quote, "just shrinks radiographic tumors" and had no, quote, "clinical evidence of benefit." It is self-evident that in the practice of oncology

medicine, tumor shrinkage, which was seen in the E2100 and other trials, is directly correlated with a decrease in tumor pain. Although tumor pain may have not been captured adequately on quality of life or adverse event scale forms on case report forms, that still does not negate the oncologic principle that response rate and progression-free survival equate to less tumor pain controlled over a longer duration.

Oncologists are well versed in managing Avastin and its side effects. We use it for the other FDA on label indications of colon, lung, renal and brain tumors, and it's been used off label per NCNN guidelines for ovarian and melanoma.

CDER argues that the drug is too toxic, but oncologists are well aware it potentiates chemotherapy and has unique vascular complications. We minimize the risk of these complications by controlling the dose, decreasing the dose where appropriate in chemotherapy, or even rolling Avastin with second or third cycles so it's safer. We manage the hypertension, and we manage the

proteinuria. So I feel like the decision to use Avastin should be left up to the patient and the oncologist.

My last comment is on the biology of cancer. Traditional pharmacologic definitions can't even describe tumor drug resistance when a drug like Avastin works upstream of the tumor. So I would like to propose that the next study performed by Genentech looks at Avastin being used in progression and further progression into second- and third-line settings so that it may ultimately have the opportunity to show overall survival. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Patrick Morgan please come to the microphone?

MR. MORGAN: I'm Pat Morgan, Shannon's husband, the Avastin super responder. There are no practicing breast cancer oncologists on this panel. Karen Midthun of the FDA said she did not want breast cancer oncologists on this panel, and this

is a breast cancer specific hearing.

However, it is too early to draw conclusions about Avastin as you're still awaiting the women on trials to die from breast cancer. This panel reviewed only responsive data, not survival rate. Avastin has proven it works for 4 stage breast cancer patients without the side effects. It's perplexing to think that you might let women die while you collect to see how many women die. Leave Avastin available for those it benefits and don't prescribe it for those it don't. That just makes sense.

What the panel was to judge is whether or not there is a clinically meaningful difference in a patient's quality of life between the patients who received Avastin and those who didn't. The committee found any such difference impossible to ascertain since the trials had not collected patient-reported quality of the data.

The FDA's oncologists are -- and please pay attention -- Richard Pazdur and his panelists' minions is upset with the accelerated approval

process. But that is not a reason to jeopardize the lives of 18,000 women on Avastin that may have been borne of accelerated approval, but the accelerated approval works. The panel should think of it as a victory. He is hung up on the word "accelerated." Whether the drug has benefits or not is irrelevant to him.

Accelerated approval was created by Congress in 1997 because it had become obvious of the FDA's bureaucratic delays regarding drug approvals and the thousands of people were dying waiting on the FDA to approve life-saving drugs. In 2003, he unilaterally decided to raise the bar for accelerated approval of cancer drugs to the same height as the standards for full approval. It must first meet his decelerated approval initially first, and this is the primary reason progress against cancer drugs reached in the clinics is stalled.

Support for his status is waning in the face of emerging science that makes continued use of his archaic approaches ineffective, unscientific and

simply wrong. Ironically, Mr. Pazdur does not review HIV/AIDS drugs so many thousands will stay alive as a direct result.

The FDA's Janet Woodcock is open to finding out who benefits from Avastin and making it available to them. The FDA Erica Jefferson (ph) states in her release that she is open to working with Genentech on proposals. Jeanne Ireland of the FDA said oncologists should use their better medical judgment when deciding what treatment is best for their patients.

Doctors should always be first-line attendants, not prejudiced panels. And Herbert Hurwitz of Duke University noted that since Avastin came to the United States in 2004, doctors have learned how to better select patients for Avastin use.

I will never understand the witch hunt against Avastin for others. Giving us three minutes is a disgrace that diminishes the credibility of this FDA and shows disrespect to the breast cancer victims. I want to finish by saying

Shannon's mom and dad --

[Time runs out.]

[Applause.]

DR. MIDTHUN: Thank you.

Would Beth Baugham DuPree please come to the microphone?

DR. BAUGHAM DUPREE: Good morning. I'm Dr. Beth DuPree. I'm a breast cancer surgeon, and I chose to come here today as an advocate and a representative of breastcancer.org.

We're asking you to consider the treatment needs and expectations as well as the preferences of women diagnosed with metastatic breast cancer. In contrast to most women with early stage breast cancer, most women with metastatic disease need continuous treatment to stay alive. Despite the desperation many people often feel with metastatic disease, they have a remarkable ability to remain able with clarity and precision to decide what treatment options are best for them.

No two women or their cancers or their treatment histories are the same. Aggregate

clinical trial results include individuals who often respond better than the average and those with other disappointing responses. We physicians are limited in our ability to figure out who will and won't get the most important benefit of any particular treatment whether in the first-line setting or in patients who have metastatic disease.

Women with metastatic disease are prepared to make these decisions, and they're willing to take greater risks and understand that other treatments have already failed them. They deserve the choice.

As a nonprofit organization dedicated to providing the most reliable, complete and up-to-date information about breast health, breastcancer.org is committed to help everyone affected by breast cancer, including their family members and caregivers, to make very much sense out of complex medical information. Hundreds of thousands of women diagnosed with metastatic breast cancer have turned to breastcancer.org to understand their available treatment options as

well as the results of clinical trials that may influence their choices.

Through the 10 years that we've been understanding and communicating with women with metastatic disease, we've learned that, unfortunately, current treatment options for metastatic cancer very often offer modest benefits and the cures are only there for a few. What does make sense treatment-wise is for any specific woman to understand the characteristics of her disease, look at the scientific evidence, and also have her weigh her expectations as far as her treatment options.

A woman's individual experience with a treatment may be different than the aggregate results from a clinical trial. Women want and need access to the widest array of beneficial, safe treatments.

Progression-free survival is a meaningful benefit. When the FDA tries to pull a medication, you're going to create a standard that insurance companies will follow. As a voice for women

diagnosed with metastatic breast cancer, breastcancer.org asks you to consider the importance of a woman's access to her treatment options. We also ask that you consider the importance of an individual woman's preferences, her perception and treatment benefits.

Please allow Avastin to be a treatment decision made by an informed patient and her physician, not a decision made here. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would the next speaker, Bob Erwin, please come to the microphone?

MR. ERWIN: I'm Bob Erwin with the Marti Nelson Cancer Foundation. The FDA's objectivity and high standards are vital to individual patients and essential to public health. Anyone following cancer drug development for long has seen the retrospective data dredges that promoters of shoddy science periodically try to sneak past the FDA, often followed by diatribes on the editorial pages of The Wall Street Journal when hype fails to

overcome good scientific review.

The dedicated professionals of the FDA, including Dr. Pazdur, are often the only significant barrier to toxic placebos in our pharmacies and 21st century snake oil salesmen promoting false hope to desperate patients and families.

However, this is not the situation that faces us in the case of Avastin today, nor is today's challenge a matter of choosing between evidence-based medicine and emotional anecdotes. Collectively, we have many years of experience with the side effects of Avastin, and nothing new is likely to be revealed today or tomorrow. We also know that Avastin, like many other cancer drugs, does not work for most women with breast cancer, but that it does work well for a fortunate minority.

Additional clinical trials of Avastin in combination with a taxane or any other chemotherapeutic agent are not likely to provide meaningful new insights on the drug's effect on

overall survival or progression-free survival. We still may not know in advance for whom Avastin will work and for whom it will fail.

This is the critical question to which we have no answer. For whom will Avastin work? Additional questions include, why have Genentech and the FDA discussed a biomarker-guided clinical trial of Avastin for months but enrollment has not begun? Why has Congress not appropriated enough money for the FDA to expand its scientific staff and infrastructure to efficiently analyze and regulate drug biomarker combinations? The lawyers really need to have a role in the drug development and approval process. And, of course, why is consideration of the relationship between price and product performance off limits to the FDA? So many elephants and so little time.

Considering all the available evidence, our recommendation is to continue the approval of the breast cancer indication under the accelerated approval mechanism, subject, however, to serious carrot-and-stick incentives to get the necessary

biomarker studies enrolled, finished and reviewed to enable better informed decisions about the ultimate fate of Avastin in breast cancer.

In addition, we believe preservation of the accelerated approval mechanism itself is of vital importance to cancer patients. We would like the FDA to use enhanced carrot-and-stick tools to make the mechanism even more valuable to patients and to clarify objective metrics of clinical performance, other than overall survival sufficient for accelerated approval, if necessary, on a disease and stage specific basis. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Heraleen Broome please come to the microphone?

MS. BROOME: Good morning. My name is Heraleen Broome. I'm a very grateful recipient of the drug Avastin. In October 2000, I was diagnosed with Stage 1 breast cancer and underwent lumpectomy, chemotherapy and radiation. Even though I had triple negative cancer, I had a very

positive attitude because it was Stage 1 and the cure rates are very high. The odds were in my favor.

In January 2003, I was informed that the cancer had returned in my breast. A planned mastectomy was canceled when it was discovered that the cancer had metastasized to my lungs. There were several tumors in my lungs, and I immediately began chemotherapy to try to shrink them. I was told that I was treatable, not curable. My oncologist, Dr. Rugo, tried two different types of chemotherapy, but the tumors were growing, not shrinking.

In July 2003, I entered a clinical trial at UCSF Medical Center under Dr. Rugo’s supervision. The drugs were OSI 774/bevacizumab. This means I have infusion of Avastin every three weeks and take a Tarceva pill daily, and results were both positive and immediate. Within a few days, all of my tumors were shrinking and many had disappeared. That was almost eight years ago. Last week, I completed my 136th cycle of this treatment.

My hope is that Avastin can remain an available treatment for people with Stage 4 breast cancer. I've met so many that have been hopeful to learn that there is life after chemo fails you, this life made possible by Avastin in my case.

I simply don't understand how the FDA can propose to find that Avastin does not provide meaningful results of meaningfully prolonged life. I owe the last seven and a half years to Avastin. Those years have seen my grandchildren grow up and they have taken me on wonderful trips to Europe and Asia, places I would never have gone without the freedom that I got from Avastin. I've helped a lot of people with cancer by encouraging them not to give up but to be positive even when they get bad news.

There's no safety problem with Avastin, so there's no reason to pull it off the market. I urge you to do everything you can to ensure Avastin continues to be available to breast cancer patients. I don't think it is reasonable for you to set a number of people that need to be alive as

a result of this drug in order to allow it to be sold. It seems to me that my life should be enough, and it's not just my life but the lives of my family, friends, coworkers and everyone I meet that are affected positively by this drug.

Please do the right thing and do not withdraw approval of Avastin. I met a gentleman who was very discouraged because his cancer wasn't improving any, and they were going to put him on this drug. He said, "Avastin." And I said, "That drug that you said, 'Avastin,' pep up when you say it because I've been receiving that drug intravenously every three weeks since July of 2003."

This was in 2008. He told me -- I said, "I don't know why I'm still here." He said, "You're still here because I was supposed to see you today."

Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Erin Ehrlich please come to the

microphone?

MS. EHRLICH: Good morning, panel. My name is Erin Ehrlich with the Colon Cancer Alliance, the nation's leading colorectal cancer patient advocacy organization. As you know, colorectal cancer is one of the deadliest and most expensive diseases to at the time. CRC is the second leading cause of cancer deaths in the United States, but early detection and treatment can yield a 90 percent survival rate.

Sadly, most are diagnosed with CRC at later stages, when the disease is very difficult to at the time. There are only a few treatment options for later stage patients, and most are not very effective. The average life expectancy of the metastatic colon cancer patient is under one year, and the 5-year survival rate is less than 10 percent.

While we understand the Avastin decision relates to breast cancer and does not directly affect CRC, we are concerned about the FDA processes in place and what we perceive as a lack

of consistent standards. Breast cancer patients are living years longer today than they were only a decade ago, mostly because of the availability of many new drugs, each of which may extend life by only a few months or reduce the risk of recurrence. We are worried that this new FDA decision-making process will affect the future of drug approvals, and decisions like the Avastin one will stifle innovation.

Our concerns are shared by many observers and experts, who fear that the U.S. has a faltering system for approving and regulating drugs and devices in this country. This summer, the Institute of Medicine is expected to release a report recommending significant changes at the FDA. Like so many others, we are hopeful that IOM can persuade the agency to change its practices. The status quo is not acceptable. If nothing is done to address the problems, it is the patients who will feel its failure most.

According to a report released recently by Northwestern University, U.S. companies are

increasingly going to Europe before the U.S. to get approval for new medicines and devices. Companies think the European new product review system is a more straightforward, transparent, faster, and less expensive one.

In a 2010 survey of medical device manufacturers, a Stanford University professor reported that products were available to patients in the U.S. a full two years after they were available to European patients, leading him to conclude that millions of Americans do not have access to the latest, most innovative medical technologies.

We must fix the regulatory process here at home so that Americans have access to the latest innovations that are safe, effective, and affordable. If we don't fix the problem, people who should not die will, the cost of healthcare will continue to rise, and innovative American companies and their jobs will disappear, only to reappear across the Atlantic.

We are concerned the FDA's Avastin decision

takes away the doctor-patient decision-making process. Metastatic patients often have few, if any, treatment options, and it should be the decision of those patients and their doctors about what side effects and risks they choose to assume.

As the voice for the 1.2 million colorectal cancer survivors in the United States, we ask the FDA to consider the importance of a cancer patient's access to drugs which help extend life or which reduce the risk of cancer recurrence as well as the individual preferences of the patient and their physicians. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Carrie Konosky please come to the microphone?

MS. KONOSKY: Good morning. My name is Carrie Konosky, and I'm the vice president of development and public affairs for the Kidney Cancer Association. I am humbled to be here today to speak on behalf of the Kidney Cancer Association and the more than 75,000 patients and families that

we serve to support the breast cancer community.

While today's hearing is not directly impacting kidney cancer patients, it is our organization's fear that the precedent set by a decision to withdraw approval for the breast cancer indication could have serious implications for all cancer patients in the future.

Our organization was founded in late 1989, and at that time there was no available therapy for kidney cancer patients. Our founder worked night and day to advocate on behalf of the accelerated approval process, which eventually led to the first available therapy for kidney cancer patients. For more than 10 years, this was the only hope that kidney cancer patients had for surviving their disease.

It is our organization's belief that it is in poor judgment for Avastin to be withheld from all patients because not everyone benefits equally. As an ethical practice, private and public payers, as well as Genentech, should continue covering Avastin for those patients who are currently

responding to it. It is the understanding of the KCA that the primary endpoint of PFS and E2100 was agreed upon in advance by the FDA, and that doubling of PFS for 12 months remains clinically relevant. It also appears possible that the toxicity of Avastin was overstated in the ODAC and FDA releases.

Speaking on behalf of the desperately ill cancer patient, it is my and the KCA's hope that the FDA will consider this action. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Helen Schiff please come to the microphone?

MS. SCHIFF: My name is Helen Schiff, and I'm speaking on behalf of SHARE leaders, a group of cancer survivors who meet monthly to discuss and debate controversial issues in breast cancer. We are affiliated with SHARE, a breast and ovarian support organization, as well as graduates from the National Breast Cancer Coalition's advocacy training program, Project LEAD.

When we started to discuss Avastin several years ago, the overwhelming majority of SHARE leaders supporting granting Avastin accelerated approval status for first-line metastatic breast cancer. Now it is just the opposite. The overwhelming majority of us think that Avastin should not remain on the market for this indication, and here are the five reasons why.

One, progression-free survival is an endpoint that benefits women with metastatic breast cancer only if it predicts overall survival or demonstrates improved quality of life. Avastin has done neither. What use is there for a drug which, in this population, does not extend life and has more toxicities, some very serious, than the present standard of care?

Two, it is absolutely essential that biomarkers be developed before a drug comes to market, not after. If Avastin does work for a subset of women, we need to know who they are. True compassion prevails only when drug companies are motivated to identify the group of patients who

actually might benefit from their drugs, thus sparing others who will not benefit the serious and life-threatening toxicities.

Three, it is one thing to give access to a promising drug. However, if that drug does not fulfill that promise, it exposes more than more patients to unnecessary harm and needs to be removed from the market immediately.

Four, it starts us down a slippery slope, at the bottom of which there is no drug regulatory approval at all, putting a drug on the market before you know if it works and for whom.

Five, we do feel, however, that the FDA should follow the same policy it did with the lung cancer drug Iressa. This would allow women already responding to Avastin-containing regimes to stay on them.

Like everyone else, we wanted Avastin to succeed in metastatic breast cancer, but we are honest enough to admit that it is not. We have seen success before with targeted drugs like Herceptin and tamoxifen that have saved or extended

lives of hundreds of thousands of women. We will not settle for less.

While I have a few seconds, just in my own name I would like to say that for every woman here testifying, there are other women who we know -- a member of our group who bled out of every orifice of her body, Jimke Vassu; another woman, Sandra -- I can't remember her last name -- in Florida who had a brain hemorrhage. So those people don't come to testify. I just want you to remember that they exist, too.

DR. MIDTHUN: Thank you.

Would the next speaker, Ivy Ahmed, please come to the microphone?

MS. AHMED: Good morning, and thank you for the opportunity to make a brief statement today on behalf of the Cancer Support Community, which serves hundreds of thousands of cancer patients and their loved ones across the United States. My name is Ivy Ahmed, and I'm the vice president of education and outreach for the organization. The Cancer Support Community did not receive any

compensation from Genentech to be here today; however, the organization does receive grant funding from the company.

We're here today on behalf of the cancer patients and families we serve every day to share our unique perspective on a matter that has far-reaching implications, not only for the future of cancer care but also for the future of all healthcare. The issues in front of the FDA today are larger than one product, larger than one indication, and larger than one treatment option for metastatic breast cancer patients.

While the FDA is considering a series of specific questions today on one product, the weight of the agency's decision will have ramifications far beyond this single product or any one indication. We're concerned that the FDA could be setting a precedent today that may have lasting implication for years to come on the cancer community at large.

We fully respect the agency's authority and the challenge of balancing safety with speed and

innovation. We also appreciate the tremendous work that the agency invests in conducting risk-benefit analyses on a multitude of products and their side effects. However, we must ask the question, at what point should decisions surrounding risk and benefit sit with the FDA, and at what point should those decisions be left to a patient and his or her doctor? At what point does the FDA have a responsibility to educate and empower patients with the facts and then leave the decisions to them with their eyes wide open?

We strongly believe that the FDA should lead a broader public discussion at this time, not about whether a specific drug has met specific endpoints, but about whether those endpoints are even the right ones in the first place.

In addition to these practical issues and implications and the objective analysis of the data, we urge the FDA to take in account the emotional consequences of leaving women with metastatic breast cancer even fewer treatment options than they have today. There is no question

that in doing so, the FDA would not just be withdrawing a treatment option for those women, but also removing hope at a time when hope of the next treatment option may be the bridge to important life events such as weddings, births, and graduations.

We must also consider the impact of any decision on innovation and further investment in the development of novel therapies for cancer and other illnesses. There must be a meaningful partnership among government, the private sector, doctors, and patients to ensure that medicines are available to consumers quickly and safely, and that they are both clinically effective and cost-effective. In a rapidly changing clinical and scientific environment, government must commit to constantly revisiting and improving the regulatory and approval process to benefit patients.

We urge the agency to actively engage consumers, patients, providers, and industry in a broader discussion about the changing face of cancer care. We offer our organization, the Cancer

Support Community, to be part of those discussions. It's clear to those of us who serve cancer patients and their families every day that the regulatory framework for approving therapies and stimulating innovation would greatly benefit from a closer examination of those who rely on it.

It is our belief that today is not the day to be making a decision on this matter until broader issues are addressed. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Terrence Kalley please come to the microphone?

MR. KALLEY: Presiding Officer Midthun, distinguished members of ODAC, courageous patients, families, friends, ladies and gentlemen, and above all, my beloved wife, Arlene, knowing that death will come early from incurable disease is devastating. The FDA has compounded this anguish by its complete indifference to current Avastin patients. The FDA has treated these women as expendable, innocent statistics in the face of

a regulatory machine on autopilot, a bureaucracy unencumbered by any ethical controls. Your callous indifference is terrifying patients. Their anxiety is excruciating, your prolonged silence deafening.

The FDA purports to base its actions on science in defiance of evidence and common sense. The highly unscientific and unethical handling of this entire Avastin saga cries out for congressional oversight and major FDA overhaul.

Let's turn to super responders, those responding well to Avastin. Despite strong empirical and observed evidence, the FDA contemptuously ignores these women, dismissively calling them "anecdotal evidence." The FDA unscientifically only considers medians from its trials. However, the FDA approach misleadingly omits the details behind the medians.

Those details are vital, changing the picture. Individual patients respond differently to treatments. Medians hide this. The super responders fall greatly above the median. The European Medicines Agency has approved Avastin.

The practicing breast cancer oncologists of the NCCN approve Avastin. Can you say with certainty that all these medical experts and patients are wrong? If there is any doubt that Avastin is keeping some of these women alive, how can you in good conscience vote against Avastin?

As many issues regarding Avastin remain unresolved, requiring further research, justice and common sense dictate that you not sentence these women to premature deaths by depriving them of their life-saving Avastin. It should not be for you, but for my wife and her oncologist, to make this life-and-death decision. Please just leave my dear wife Arlene alone to continue taking her medication without any interruption of existing insurance. Is this asking too much?

Make no mistake. This hearing is a death trial, not of Avastin, but of these women who rely on Avastin to stay alive. You are each personally responsible for the consequences of your own vote. If you vote against Avastin, do not count on insurance companies and Medicare to provide

coverage for Avastin. A vote against Avastin by each of you is a vote against thousands of women.

It has fallen to organizations such as my own, Freedom of Access to Medicines, staffed and funded solely by patients, their families, and friends, to fight for these Avastin women, to file the Freedom of Information Act request with the FDA. We organized the protest outside the FDA despite the FDA's attempts yesterday to silence us.

When, heaven forbid, just one patient is denied this drug, Avastin will become a household word in America. As America watches you and the FDA, reversing your prior "No" votes on Avastin will take humility, wisdom, great courage. Let not history show that you --

[Time runs out.]

[Applause.]

DR. MIDTHUN: Thank you.

Would Christine Brunswick please come to the microphone?

MS. BRUNSWICK: My name is Christine Brunswick. I'm vice president of the National

Breast Cancer Coalition. I was diagnosed with breast cancer 20 years ago and am currently living with metastatic disease. I can personally attest to how devastating this disease is.

NBCC, along with thousands of advocates, is dedicated to Breast Cancer Deadline 2020 to refocus research on preventing breast cancer and preventing metastasis by January 2020. We look to the FDA to help achieve that goal. I'm here on behalf of NBCC to support FDA's decision to remove breast cancer as an indication for the drug Avastin.

Avastin has been shown to be unsafe and ineffective for breast cancer patients. The FDA's decision on Avastin must be based on scientific evidence from well-done trials and cannot be based on any one individual story, no matter how compelling. This decision cannot be driven by anecdotes. It must be driven by science. This decision must be made for the greater good and on a public health basis.

The addition of Avastin failed to demonstrate a significant improvement in overall

survival. This may not be what many of us wanted to hear, but we must accept and act on evidence or we will never make the needed progress we so desperately want.

In 2008, NBCC expressed concern about the accelerated approval of Avastin. We now know that women died because of this drug. We know the follow-up studies confirmed that the drug is not effective for breast cancer patients and that it increases serious adverse effects.

Women deserve access to treatments that scientific evidence proves are effective. Avastin does not meet that standard. We fully understand how painful it is that we do not yet know how to cure metastatic disease, but we need to focus on doing more good than harm. The FDA's decision to withdraw the indication supports that approach.

This decision must be about one investment only, the investment in saving lives. What we are currently engaged in propels us backwards, spending enormous resources defending a drug that does not live up to its promises. It does not significantly

keep the disease at bay, it surely is not a cure, and it does not extend life. The drug does raise false expectations and does detract from focusing on other research that may produce effective, life-saving drugs.

Should we be defending and promoting a drug that fails patients in every way? Should we spend time and lives on drugs like Avastin that do nothing to save women from the devastation of breast cancer? We really do deserve more.

The data show that Avastin should no longer be used in the treatment of this disease, and the FDA's decision to rescind should stand. Thank you.

DR. MIDTHUN: Thank you.

Will the next speaker, Kimberley Jewett, please come to the microphone?

MS. JEWETT: I am completely disgusted to have to follow somebody like that. She apparently has not listened to the many women who are standing here today and have benefited from Avastin.

[Applause.]

MS. JEWETT: My name is Kimberly Jewett, and

I am a breast cancer survivor. Three years ago, at the age of 31, I was diagnosed with breast cancer. At that time, I can remember feeling overwhelmed by the treatment process and was mostly concerned for my then-6-year-old daughter and 4-year-old son.

At that time, the most difficult struggle I faced was the effects my diagnosis had on my two young children. My daughter always wondered if I was going to die, the daughter that sat at her bedside on her knees praying to God that her mommy had the strength to fight breast cancer, a child who wanted her mommy to help her grow and develop into the young woman she would someday be.

These types of moments were one of the many emotional and physical emotions I endured while undergoing my treatment process. But I must point out that those emotions were tied with choices, choices that came from recommendations, and recommendations that my medical team provided me with. And with those recommendations came choices.

I made the choice with my medical team to have a mastectomy. I made the choice to have

reconstruction and chemotherapy. And all of my choices led me to where I am today, just like the many women who have made the choice, with their doctors, to take Avastin.

When we look at the many side effects that surgeries have, steroids, chemotherapy, and even basic aspirin, I feel Avastin is no different. It is a drug that has side effects, and to me it is a drug that is a choice, just like many other options a cancer makes during the cancer diagnosis.

I have met many women who have breast cancer, young women that do not have the opportunity to have children, and unfortunately, the women that are metastatic. And what I have learned from my diagnosis is, I am fortunate to be standing here in front of all of you today.

I am a survivor and an advocate for the women who do not have a voice to tell you they are here because of their choice to take Avastin, the many women who are not here, sadly enough, who had that choice to take Avastin and had one more day with their families. And I can tell you that

today, if I became metastatic, I, too, would want that choice to take Avastin to have one more day with my children.

I sincerely hope that my personal breast cancer battle will serve as a voice for the many people who have choices and would do anything they can to continue to have that choice to have one more day with their families.

[Applause.]

DR. MIDTHUN: Thank you.

Would Vernal Branch now come to the microphone?

MS. BRANCH: Hello. My name is Vernal Branch, and I represent the Virginia Breast Cancer Foundation and Breast Cancer Action. We carry the voices of people affected by breast cancer to inspire, compel the changes necessary to end the epidemic. We represent members nationwide who believe that patients should come before profits.

Metastatic breast cancer is a heart-wrenching diagnosis, and we believe we need more effective and less toxic treatments. Like many

others who care about people affected by breast cancer, we would have been pleased if data presented showed Avastin to be a more effective treatment for metastatic breast cancer than other drugs already on the market.

Unfortunately, the existing evidence from randomized controlled trials conducted by the drug's manufacturer has demonstrated that Avastin has not lived up to the initial hype. Trials completed demonstrated some improvement in progression-free survival. We remain convinced that it is not enough to justify FDA approval for treating metastatic breast cancer. Furthermore, subsequent trials failed to show the same progression-free survival in the original study.

The goal is to obtain statistically reliable evaluation of a drug that represents a clinically meaningful result that yields favorable benefit-risk evaluation. Trials involving Avastin have simply not yielded those type of benefit-risk ratios.

Avastin does not meet several criteria. The

major problem with Avastin is that it has not shown increased overall survival for patients that took the drug. Overall survival was not used as the endpoint in the studies, which means that we have no data on whether patients live longer overall when taking the drug. Overall survival is the most beneficial measure for patients, however.

Quality of life is very subjective, but some of these diminished capacities for quality of life includes gastrointestinal perforation, splitting of wounds and organs, internal bleeding, high blood pressure, congestive heart failure, heart attack, and stroke.

We understand that Genentech is planning on additional trials. While we are not opposed to new trials, we do believe Avastin should not retain its approval while further study is conducted. If there is new evidence, Genentech should follow the existing process.

FDA must require that pharmaceutical companies sell more than hope to patients. We recommend that FDA stay the course with its

December decision to revoke accelerated approval of Avastin until new evidence is produced that shows the improvement of overall survival. Thank you.

DR. MIDTHUN: Thank you.

Would the next speaker, Christi Turnage, please come to the microphone?

MS. TURNAGE: Good morning. My name is Christi Turnage. I am a wife, a mother of four, an advanced practice nurse, and a breast cancer advocate who is living with metastatic triple negative breast cancer. I am speaking today on behalf of my family and the more than 11,000 people who have signed the petition that I started online to keep Avastin, most of those being patients.

I was diagnosed originally in June of 2006 with Stage 2 breast cancer, and by 2008 it had spread to my lungs. My daughter was only 3 years old at that time. After four chemos and Avastin treatments, I had no evidence of disease, and after seven months, I was on Avastin alone.

Talk about an increased quality of life. I had hair again, which made my life for my children

so much easier. They didn't think I was sick any more. It was very distressing to a toddler for a mom to look that poorly. I have been on Avastin for three years this month and have had 32 months of no progression. That is priceless.

I have many friends who have experienced this and more, many more years, ladies with six, seven, eight years. And while I realize this may not be the norm of what was found in the trials, these cases exist. We exist.

There has been a discussion about whether the improvement in progression-free survival is clinically meaningful for patients. As a patient living with this disease, I would say most definitely it is. I believe that the definition of a clinical benefit is a personal question that each patient needs to answer with their doctor. Every day of no disease progression amounts to a day of living, a day to love on my children, a day to maybe see them grow up, to see a wedding, a graduation, a kindergarten; starting kindergarten I was able to see.

Some experts say the gold standard is overall survival, but this is a controversial subject, even among oncologists. It was found that only 1 in 5 breast cancer patients showed overall an survival, and overall survival is seldom used as the primary endpoint. Why is Avastin being held to a higher standard than others?

As far as toxicities and side effects, I have a sore throat and I'm really tired. I raise four children and I work as a nurse. And I know other people have serious side effects, but that's only 4 percent. Less than 1 percent of people die from this drug, and only 4 percent have the serious side effects. And, no, I wouldn't want one of those side effects, but if I don't have this drug, I know that I will have death. I mean, that's obvious. So that's a no-brainer for me to take this drug when I look at my options.

I'm just going to skip on and just show you a few of my younger friends that have benefited from Avastin. These are ladies that are in their 30s. Erin had stayed on Avastin for two years; it

was able to give her enough time to get on the trial. She did great. And then Jen is 34 years old, and as she says, “Avastin may not add to her overall life expectancy, but it allowed her to have progression-free” --

[Time runs out.]

[Applause.]

MS. TURNAGE: Here’s the petition.

DR. MIDTHUN: Thank you.

Would Elda Railey please come to the microphone?

MS. RAILEY: Good morning. I am Elda Railey, co-founder of the Research Advocacy Network, an organization founded to advance patient-focused research.

Respecting the patient perspective in the research dialogue is essential to improving patient care, and I appreciate the opportunity to share thoughts with you today as we all work together to do just that, improve patient care.

We are encouraged by the FDA’s efforts to set standards for agents approved with progression-

free survival as an endpoint. Standards and consistent processes for agents approved with accelerated approval are also needed.

What is the level of benefit and toxicity that must be met for accelerated approval? Are the criteria different for targeted therapies than for chemotherapy? Is the level of benefit and toxicity used in primary care cancer versus metastatic cancer considered consistently? Many metastatic patients are willing to deal with greater toxicities than those in earlier treatment stages.

Recently the Research Advocacy Network presented a poster at the ASCO annual meeting that discussed our findings about risk-benefit tradeoffs and decision-making around biomarkers in this patient population.

There are many patients that have benefited from Avastin, as you've heard today. Clinicians also state that they have patients who have benefited from taking Avastin. This level is exceeding the median 5.5 months found in E2100, the trial that merited accelerated approval.

Removing the metastatic breast cancer indication will mean current and future breast cancer patients who could benefit from this agent will not have access without third party payer reimbursement. Dr. Pazdur has even stated that he wants to find out which patients benefit from taking this agent. We will only find that out through further research. And there is research ongoing to find biomarkers for the benefit and toxicity.

We applaud the FDA critical path for initiating a funding program for novel biomarker research and hope the proposals to address this very issue of a companion diagnostic will be funded by this program. But this funding program alone is not enough and is not targeted specifically to this issue.

Previously, we asked for a “state of the science” meeting that would allow for researchers to discuss and share what they’ve learned. The outcome of this meeting would be strategy and a timeline for answering this specific question.

The people most affected by this decision are current and future breast cancer patients. In addition, patients diagnosed and being treated with Avastin for other cancers will also be affected by this decision. It is incumbent upon the scientific and regulatory communities to foster an atmosphere of collaboration and scientific integrity and inquiry to solve this issue for the benefit of cancer patients. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Tim Turnham please come to the microphone?

MR. TURNHAM: My name is Tim Turnham, and I'm the executive director of the Melanoma Research Foundation. I admit I have little information about the efficacy of Avastin in breast cancer and offer no opinion regarding the level of clinical benefit needed for approval. But I will say this. My concern is has the approval process for this drug been clear, consistent, and reasonable?

This past spring, for the first time in

13 years, the FDA approved a new drug for metastatic melanoma. Despite this advancement, melanoma patients desperately need additional and better therapies. The basic science of melanoma is understood to the point that these therapies are easily envisioned, so now we must bring these therapies quickly into the clinical setting. And a critical part of accelerating drug development hinges on the regulatory process, a process that represents a growing percentage of the time and expense of drug development.

The FDA has issued a white paper on improving regulatory science, yet no improvement will have significant impact unless the criteria for approval are clear, consistent, and reasonable.

The FDA granted accelerated approval for Avastin and made full approval contingent on studies confirming safety and clinical benefit in the form of progression-free survival. Genentech met these criteria. The company then requested full approval, with the reasonable expectation that approval would be granted. Instead, the company

was informed that the previous approval would be withdrawn.

Again, I have no opinion about the merits of this drug in breast cancer. I do believe, however, that for the FDA to set forth criteria for approval and then change those criteria reflects an approach that may have a chilling effect on drug development. At the very least, industry may be less willing to consider much-needed changes in their approach to clinical trials.

We are seeing these days new discussions on the ethics of clinical trial design, with a push for crossover provisions, particularly when the control arm offers little efficacy and the trial arm is showing promise. Crossover, however, makes demonstrating overall survival very difficult, and makes progression-free survival more significant. Withdrawal of approval of Avastin because the studies failed to achieve a sufficient, yet unspecified, level of PFS will put additional pressure on industry to avoid crossover despite the impact on patients in those trials.

Equally significant is the issue of combination studies. Melanoma researchers agree that true progress will likely be found in combining drugs, and that the best combinations include drugs that are not yet approved. But industry is reluctant to engage in such trials, citing regulatory challenges. If the current system is perceived as being unclear or inconsistent, how likely is industry to engage in a regulatory path that is different or novel, regardless of the potential benefit offered to patients?

As you make your decision regarding Avastin, I urge you to consider what that decision says about a regulatory process that is essential to ensuring that new and better treatments are available to patients. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Carolyn Law please come to the microphone?

MS. LAW: I come this morning as a breast

cancer survivor, at least, a survivor so far. Thankfully, I have never had to face metastatic cancer, but I watched my mother and a good friend die from it. Their lives revolved around doctor visits, and there was never any good news.

Everyone I know who has had Stage 4 any kind of cancer has died, and usually with a significantly declining quality of life: sick, in pain, weak, barely able to get off the sofa, although statistically labeled “surviving.”

I personally knew one recipient of Avastin who, on her deathbed, was given it as a last resort for a different type of cancer. There was a quick and dramatic reversal of her condition. The results were spectacular. Yes, she died anyway about a year later, but in the meantime she had a sports-filled life, virtually doctor-free, and a vibrant quality of life.

My father was a physician. He told me there is a big difference between prolonging life and prolonging death. With my mother, I watched as her death was prolonged. With the person who took

Avastin, I saw how wonderfully her life was prolonged. The two were vastly different.

So if you knew you were to have one year of life left, would you choose a steady decline of being sic, weak, frail, generally unable to participate, needing increased assistance, and being a heart-wrenching sight for your family to endure; or would you want to continue your activities and outings and sports and doing the things that bring you and your family pleasure, and living a vibrant life?

Today we have heard articulate testimonies from doctors and patients about the effectiveness of treatment and quality of life provided by Avastin. There is something to this drug. It holds great promise. Yes, do more research. But in the meantime, please keep this available to women with metastatic breast cancer. Do not deny them or withdraw their access to this drug. Do not deny me this choice as I, too, might need that option someday.

You hold people’s lives in your hands.

Please do not take that responsibility lightly. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Karen Zinka please come to the microphone?

MS. ZINKA: My name is Karen Zinka. I work for Men's Health Network, but I am here today speaking on behalf of Christy Larch. Christy Larch is a 43-year-old metastatic breast cancer survivor and mother of two in Washington State. She was treated with Avastin and paclitaxel chemotherapy. She's a full-time attorney serving victims of domestic violence, and that is why she cannot be here today, but she asked me to share her thoughts.

She requests that the committee recommend that the FDA reverse its decision to withdraw approval of Avastin's metastatic breast cancer indication, specifically, Avastin's pairing with paclitaxel. Genentech should be directed to conduct further studies of metastatic breast cancer patients who have direct experience with the

Avastin and paclitaxel combination to further assess progression-free survival and clinical benefit.

This is a very complex issue requiring further research. There is substantial anecdotal from metastatic breast cancer patients and providers that indicates this combination results in increased progression-free survival as well as prolonged patient life. A study that includes data from patients and their doctors with Avastin and paclitaxel experience is appropriate.

Women living with metastatic breast cancer constitute a significant and substantial contingent. For these women, any treatment that will increase the efficacy of their chemotherapy regimen, impede tumor growth, and increase their survival lives must be given further consideration. Individuals living with metastatic breast cancer need access to any treatment that may accomplish these goals.

Women with metastatic breast cancer are vital, productive members of our economy. Their

incomes and federal tax brackets range from the top to the bottom of the schedule. They all contribute to this country's economic vitality. Those fortunate to have private insurance may pay for both their insurance as well as annual deductibles and co-pays, contributing further to the economy. They fill necessary paid positions, they volunteer, they raise children that may otherwise be dependent upon public resources, and they pay their taxes. At this time, the decision whether to use an Avastin and paclitaxel combination is appropriately determined by an individual and her medical oncologist, and we would hope to keep it that way.

Christy is one of many women who have successfully treated with Avastin and paclitaxel combination. She appears to be proof of a clinical benefit. She is certainly proof that side effects and potential side effects are manageable. Her medical oncologist took quite reasonable precautions before and throughout her treatment to ensure her Avastin use was safe and appropriate. Her cancer was greatly reduced by the time she

ended her treatment, approximately six months after it began.

Contrary to the very limited study results, Avastin has become a very popular weapon in the fight against breast cancer. There are women with triple negative metastatic breast cancer who have very few treatment options. For some of these women, Avastin has been their means of true survival since they learned of it.

Thanks to Avastin, Christy's children have their mother, her friends and community have her around, and she is able to continue to serve her clients. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Maureen Thomas please come to the microphone?

MS. THOMAS: Good morning. My name is Maureen Thomas, and I reside in Winston-Salem, North Carolina, and I am a 5-year cancer survivor.

I come before you today as an advocate for the use of Avastin to treat metastatic breast

cancer. Like most drugs, Avastin is said to cause a variety of side effects. However, in my personal journey of recurrent metastatic breast cancer with lymph node involvement, I have experienced very minimum side effects.

While using this drug, my PET scan has been normal and the cancer has not spread to other parts of my body. This drug has worked well for me for the last three years, and I am very concerned about patients like myself who are receiving this drug now and may not be able to receive it any longer.

I humbly request your consideration in approving Avastin for the continued use to treat metastatic breast cancer. It is my belief that these patients should not be denied this drug. Even though it is costly and has many side effects, we should be able to sign a waiver that states we are aware of the side effects and are willing to take the risk. I am living proof that Avastin does work.

During my cancer battle for the last five years, I have had the best care from Dr. Judy

Hopkins, Dr. Slatkoff, and Carol Holt, P.A., and the nurses at Kernersville Oncology in North Carolina. And I have had the support of my husband of 25 years, my children, grandchildren, my other family members, my pastor, Reverend Cliburn, and my church family and friends. And I thank them all for their continued support. I know, with Jesus Christ, all things are possible.

I have a petition with over 900 signatures requesting the FDA's approval of this drug. This approval is very important to breast cancer patients like myself so that we will continue to have treatment with this drug to control cancer, improve the quality of life, possibly extend life, and provide hope.

I appeal to this committee to reexamine the pros and cons of the study done on Avastin and allow those of us who have not been adversely impacted to continue to have access to this medication.

Thank you for the opportunity and for what I hope will be a favorable action by the committee.

Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Theresa Morrow please come to the microphone?

MS. MORROW: Good morning. My name is Theresa Morrow, and I'm speaking today on behalf of Men's Health Network. We are a national nonprofit advocacy organization whose mission is to reach men and their families where they live, work, play, and pray.

We urge the committee today to carefully consider the well-being of women and their families affected by metastatic breast cancer to ensure that they have access and to ensure that they continue to have access to a broad range of treatment options. We believe Avastin should remain an available option to women with metastatic breast cancer.

This issue does not affect women in isolation. It has serious implications for husbands, loved ones, families, and communities.

Men and their families want the best care, management, and support for their wives, mothers, sisters, and friends. And it's important to remember, of course, that men can get breast cancer, too.

We strongly believe that treatment decisions should be made between an individual and their healthcare provider. That decision should be made after a thoughtful discussion about benefits and risks -- for the treatment or therapy.

Today you have heard from a number of women, patients who are living life to the fullest thanks to Avastin. We urge you to take these women into consideration, along with the thousands of other women who have succeeded on Avastin.

Men's Health Network seeks to support and promote optimal care and access to effective treatments. Even if Avastin is available for use off-label, many will not be able to afford the drug without coverage by insurance companies.

Where possible, we should also avoid action that would stifle medical research and innovation

and limit access to life-saving therapies for women, men, and their families. We stand here concerned about the long-term implications of these decisions 3, 5, and 10 years down the road.

As we move toward more personalized treatments for patients, Avastin should remain available to metastatic breast cancer patients. It may allow a woman 2 months, 2 years, or 10 years longer with her husband, children, and grandchildren. Thank you.

[Applause.]

DR. MIDTHUN: Thank you.

Would Stephan Davis please come to the microphone?

MR. DAVIS: Good morning. Thank you for the opportunity to speak to you. My name is Steve Davis. I'm not being paid by anyone to be here.

I'm here to represent my wife, who lost her battle with breast cancer and passed away in April after a 10-year battle, and participated for over 2 years in the Avastin arm of the RIBBON trial. I'm here today to let you know in very simple terms

it is quite possible if she had not done this, her life may have been cut shorter by those two years.

In her own words, after she had been on the protocol for approximately six months, the scan showed all spots resolved. Anne was a teacher, a great mother to our children, and a wonderful wife to me. What the RIBBON trial did was put the cancer in remission for those two years and allow her to keep living her life in the most normal way possible.

One of her goals was to make our son's wedding, and she did. I still had my wife, and we kept making good memories. Side effects from the treatment were managed and minimized, and I think it's important not to forget that most every protocol for cancer treatment has side effects. Some are worse than others, but let's face it; it's Stage 4 cancer. Anne was not about to give up, and frankly, there were times during this illness she became too sick and she was only given Avastin. Anne spent much of her life helping people.

Isn't that why we're here today? When

you're given a diagnosis such as Stage 4 cancer, if you choose to fight it, you will more than likely at some point run out of options. And, see, knowing Stage 4 cancer is almost always fatal, the choice to participate in the trial was not a hard one to make.

Anne was made aware of potential side effects with every new treatment, but that did not deter her determination to fight the disease with everything she had. She did everything right. All her mammograms on time, all her standard treatments, and when she was put on the Avastin trial, she had amazing results. She still died, but her quality of life during the trial made it all worthwhile, and we would not have changed a thing.

Please ask yourself, if this happened to you or anyone in your family or extended family, if the choice to do this would be important to you. We all so desperately want a cure, sometimes we equate success with living longer. Perhaps we should look at quality of life as a marker of success because

we don’t have a cure.

Anne would have done this all over again. I am asking you in her name to allow Avastin to retain its accelerated approval status so it can remain a choice for everyone with Stage 4 breast cancer.

Thank you for your time.

[Applause.]

DR. MIDTHUN: Thank you.

If Diana Zuckerman has arrived, would she like to come to the microphone, please?

DR. ZUCKERMAN: I’m Dr. Diana Zuckerman, president of the National Research Center for Women and Families and our Cancer Prevention and Treatment Fund. I come here with the perspective of someone who’s a fellow at the University of Pennsylvania Center for Bioethics. I also formerly was trained in epidemiology at Yale Medical School, was on the faculty at Yale and Vassar, and did research at Harvard. And I’m also here as someone who has lost dear friends to breast cancer.

When the FDA made a decision to approve

Avastin for Stage 4 breast cancer in an expedited manner, that was a risk that they took. And they took it in order to make it available on the hope that it would be effective, with the understanding that it would have to be proven effective in survival and/or quality of life.

Unfortunately, that did not happen. And it would have a terribly chilling effect, it seems to me, on the FDA to make these kinds of risky decisions if they then were not able to rescind approval or ask for additional research in order to extend approval. So for that reason, I'm here to support the FDA's decision to rescind approval, but also to talk about what we can do to help the women who are already on Avastin and seem to be benefiting from it.

The research shows that for every woman in this room who seems to have had a wonderful experience with Avastin as well as for survivors of those women, there is at least one if not two women who had a very different experience because the research shows that Avastin does not improve

survival and does not improve quality of life.

So that means for every woman who had a 2-year extension of her life, apparently, there's at least one woman, and possibly two women, who died sooner than they would have if they hadn't had it. And for that reason, we need to be very careful what we do.

But I do ask that Genentech continue research, figure out who are the women who are going to benefit so that when a woman has to make this decision in the future, she'll have a good chance of benefiting from Avastin, not being harmed by it. And meantime, since the company has made a lot of money on this drug through this expedited approval, I ask that Genentech make the drug available for free for the women who are on it so that they can continue to be on it if it benefits them.

Thank you very much.

DR. MIDTHUN: Thank you.

If Patricia LoRusso has arrived, would she like to come to the microphone now?

[No response.]

DR. MIDTHUN: I don't think she arrived. I want to now express my thanks to you and all the other participants during this portion of the hearing. Presentations by members of the general public have now concluded, and there will not be any additional presentations from the audience.

We will now take a 15-minute break, and this hearing will resume in 15 minutes, which will be at 20 past 10:00. Thank you.

(Whereupon, a recess was taken.)

Affirmative Presentation by CDER

DR. MIDTHUN: All right. We are now moving onto the next portion of the hearing, which will be a presentation by the Center for Drug Evaluation and Research. They will have a two-hour period in which to make their presentations. They will also have a light system. The light will go yellow when there are five minutes remaining. And then when it turns red, their allotted two hours are over. So we will start with that now.

Dr. Pazdur?

DR. PAZDUR: Thank you. Good morning. I am Dr. Richard Pazdur, and I am the director of the Office of Oncology Drug Products in FDA's CDER, and that is Center for Drug Evaluation and Research. I have been with the FDA for 11 years. Prior to joining FDA, I was on the faculty at the University of Texas MD Anderson Cancer Center in Houston, Texas for 11 years. I was a professor there and a practicing oncologist.

I would like to personally thank all those who share their views on today's subjects with the agency. Few of us here today have not been touched personally by cancer. We at CDER are aware of the human toll caused by breast cancer. All of us would like to see new, safe, and effective treatment options for patients.

While we acknowledge the pain and suffering caused by cancer, our job in making decisions about drug approval is to focus on the available scientific evidence. Our regulatory decisions are based on data from adequate and well-controlled clinical trials. They are not based on

consideration of the drug's cost or decisions by third-party payers regarding reimbursement.

During our presentations, my colleagues and I will explain why CDER has proposed to withdraw approval of Avastin's indication for the treatment of patients with metastatic breast cancer. We will explain the scientific basis for our conclusion, that, number one, Genentech's required confirmatory trials failed to verify a clinical benefit of Avastin in treating patients with metastatic breast cancer, and two, the totality of the data submitted to the FDA show Avastin is neither safe nor effective to support the breast cancer indication.

Finally, we will explain why the law, the science, and the public health policy all counsel against permitting Avastin's breast cancer indication to remain on the label while Genentech designs and conducts additional studies.

Avastin was first approved by FDA in 2004 and is currently approved for a total of five oncology indications. CDER's proposed withdrawal of the indication for metastatic breast cancer has

no impact on the other four approved indications. CDER is not proposing to remove Avastin from the market.

Avastin's indication for breast cancer is limited to use in combination with one specific chemotherapy drug, paclitaxel, for the treatment of HER2-negative metastatic breast cancer in patients who have not previously received chemotherapy for metastatic breast cancer.

While CDER and Genentech disagree about many issues to be discussed today, one issue about which there is no dispute is that Avastin has not been demonstrated to improve overall survival in patients with metastatic breast cancer in clinical trials. Five clinical trials in breast cancer have failed to demonstrate an overall survival benefit when Avastin is added to various chemotherapy regimens.

Further, the available data fail to demonstrate that Avastin improves health-related quality of life outcomes in patients with metastatic breast cancer. If data submitted to the

agency demonstrated any of these benefits, an improvement in overall survival, health-related quality of life, or a substantial improvement in progression-free survival, we would not be here today.

We are aware that some patients and their physicians believe Avastin has provided a benefit to individual patients in the treatment of breast cancer. For the indication we are discussing today, Avastin is used in combination with paclitaxel, a known effective chemotherapy agent. When an individual is administered both drugs together, it is not possible to ascribe any benefit to Avastin alone. That is why the clinical trials included a randomized comparison of the combination treatment versus paclitaxel alone.

Now, I'd like to provide you some background on how we determine a drug provides clinical benefit in treating cancer and why we approved Avastin's breast cancer indication originally.

When approving any drug, the agency must conclude that the drug offers clinical benefit to

patients. Clinical benefit is a direct, tangible benefit to patients. It generally means prolonging patients' lives or improving the quality of lives. In determining the net benefit of the drug, we must assess the type and the magnitude of the benefit, and weigh that information against any safety concerns or risks.

Any improvement in overall survival is generally considered the gold standard endpoint in oncology trials. In fact, in 1999, ODAC recommended that we require drugs to demonstrate an improvement in overall survival for approval for first-line metastatic breast cancer. Over the past decade, oncologists and patients have asked the agency to consider other endpoints in breast cancer and other types of cancer. We have been willing to do that, provided the data for the alternate endpoint are clear and support a favorable benefit-risk determination.

One alternative endpoint is progression-free survival, or PFS. PFS generally refers to the time from the start of treatment until disease

progression or death from any cause. PFS is primarily determined by evaluating radiographic scans of tumors to determine whether they are growing.

In the trials under discussion today, the primary endpoint was PFS. It is important to keep in mind that although PFS includes the word "survival," it does not mean that patient's life will be extended. An improvement in PFS does not necessarily correspond with a longer overall survival, or an improved prognosis, or improved quality of life. Therefore, in making risk-benefit decisions for drugs whose benefit is defined by PFS, we must carefully consider the magnitude of the effect.

To illustrate this point, an improvement in overall survival represents a clear direct benefit to patients. They live longer. An improvement in overall survival of a given magnitude has a clearer meaning in a benefit-risk analysis than the same magnitude of improvement in PFS. For this reason, in guidances, in publications, and in ODAC

discussions, we have emphasized that the magnitude of PFS improvement must be substantial to support approval, and it must outweigh the risk associated with the treatment. In addition, CDER has consistently emphasized that a demonstration of statistical significant improvement in PFS may not translate to a favorable risk-benefit decision.

Another endpoint examined in oncology trials, which you'll hear about today, is objective response rate or ORR, defined as a proportion of patients with tumor-sized reduction of a pre-defined amount for a minimum time period. It reflects activity in tumors, but like PFS, an improvement in ORR may not, or may, correspond with longer survival or other clinical benefit to patients.

One more term you'll hear about today is "hazard ratio." This is the same concept as relative risk. It compares the risk of an event or outcome in one group with a risk of that event or outcome and another group. A hazard ratio of 1 would indicate that the risk in each group is

identical. In clinical trials, a hazard ratio less than 1 generally indicates a favorable effect was seen in the treatment arm.

As you will see from our later presentations, data from one clinical trial, E2100, suggested that adding Avastin to paclitaxel improved progression-free survival by a median of five and a half months with a hazard ratio of 0.48 without an accompanying improvement in overall survival. However, another trial, AVF2119g, which was performed in a second-line setting, failed to show either an improvement in PFS or overall survival when Avastin was added to chemotherapy. In other words, one trial suggested a fairly large improvement in PFS, but no overall survival, while another showed no benefit at all.

We sought expert advice from ODAC in December of 2007 in evaluating these data. The members of ODAC carefully reviewed and vigorously debated the interpretation of this data. In the end, ODAC voted 5 to 4 against approval of Avastin for this indication.

Given the promising but yet unconfirmed benefit seen in E2100, CDER believed that accelerated approval was an appropriate regulatory option with a requirement for a post-approval study to confirm the magnitude of PFS seen in E2100 or to demonstrate some other direct clinical benefit to patients. Genentech agreed to this path forward.

As part of the agreement of accelerated approval, Genentech identified AVADO and RIBBON 1 as the trials that would provide the confirmatory evidence to verify clinical benefit. This verification could have been demonstrated as an improvement in overall survival, an improvement in health-related quality of life, or confirmation of the magnitude of the PFS benefit observed in E2100.

We now have reviewed complete data from AVADO and RIBBON 1, as well as an additional trial, RIBBON 2, which you'll hear about in a later CDER presentation. The totality of the data available today paints a very different picture from the one available to FDA at the time of the accelerated approval of Avastin for breast cancer.

We now have five randomized trials of Avastin added to chemotherapy in breast cancer trials involving more than 3,500 patients. We have carefully reviewed this data and conclude that no trial demonstrated an improvement in overall survival, no trial has demonstrated an improvement in health-related quality of life, and no trial has confirmed the magnitude of benefit in PFS observed in E2100 that led us to the approval of the breast cancer indication.

After very carefully considering all of the available data, we've determined that the benefits of Avastin for the treatment of patients with metastatic breast cancer do not outweigh its serious and potentially fatal risks. You will hear more about the serious risks associated with Avastin in our later presentation, but in short, Avastin can cause very serious complications, including intestinal perforation and hemorrhaging.

Approximately 1 percent of patients in controlled trials of Avastin in breast cancer appeared to have experienced Avastin treatment-

related mortality. And even more common risks that were not fully tracked in the studies at issue can lead to a detriment in the quality of life and can limit options for later salvage therapy with other agents.

In July 2010, we once again sought expert advice from ODAC in reviewing and interpreting the available data for Avastin in breast cancer. Following a careful review and discussion of the available data, the members of the committee recommended nearly unanimously, 12 to 1, that the indication for breast cancer be withdrawn.

Following the July 2010 ODAC meeting, Genentech proposed to perform an additional clinical trial in which patients would be randomized to receive either paclitaxel or paclitaxel plus Avastin. Genentech proposed that this trial would confirm clinical benefit of Avastin in breast cancer and that the breast cancer indication should remain on Avastin's label while this trial is designed and conducted.

Because the pre-selected confirmatory trials

have failed to verify clinical benefit, and the available data do not support a favorable benefit-risk balance for Avastin in breast cancer, it is not appropriate to continue accelerated approval while Genentech tries to conduct another trial to establish clinical benefit.

It is likely that any new study will take years to complete and the available data simply do not suggest that a new study is any more likely to show the magnitude of benefit observed in E2100. The agency must show an appropriate degree of flexibility in making new promising drugs available to the American patients with serious and life-threatening diseases as early as possible.

The accelerated approval regulations, which you'll hear more about in a moment, provides us that flexibility. But there is a tradeoff here. Under accelerated approval, FDA can approve promising new treatments under the condition that post-approval studies must be conducted in a timely manner to verify clinical benefit to patients. But FDA may expeditiously withdraw approval if clinical

benefit is not confirmed, in the interest of public health.

In 2011, the decision on Avastin in breast cancer can no longer be based on the results of E2100 alone. The decision must be based on the totality of the evidence from all of controlled clinical trials.

The totality of the evidence points very clearly to the conclusion that Avastin has not been shown to be safe or effective in treating breast cancer. Accordingly, CDER has proposed to remove the breast cancer indication from Avastin's label in the interest of individual patients and the public health.

I would now like to welcome Abigail Brandel from the Office of Chief Counsel, who will discuss the legal framework for accelerated approval.

MS. BRANDEL: Good morning. My name is Abby Brandel. I'm a lawyer in FDA's Office of Chief Counsel, representing CDER in this proceeding. The purpose of my presentation is to provide the legal context for today's hearing.

There are two statutes relevant to this proceeding, the Public Health Service Act, or PHS Act, and the federal Food, Drug, and Cosmetic Act, or FDCA. Avastin is a biological product, and therefore, was approved under the PHS Act. FDA regulations are also relevant. They are located in Title 21 of the Code of Federal Regulations.

There are two mechanisms for approval of a biological product, regular and accelerated. The accelerated approval pathway was created in the early 1990s. It is reflected in the Food, Drug, and Cosmetic Act, but many of the details of the program are set out in FDA regulations.

With respect to biologics like Avastin, those regulations are located in Subpart E of Part 601. Regardless of whether approval is regular or accelerated, the same substantive standards for safety and effectiveness apply. Under Section 351(a) of the PHS Act, a biologic must be shown to be safe, pure, and potent in order to be approved.

The concept of potency has long been

interpreted to include effectiveness. No biologic is absolutely safe. There is always some risk. FDA, therefore, decides whether a biologic is safe by weighing the risks against the benefits. The other key point to remember is that the risk-benefit analysis of a product is not static. It can change over time, based on the available data.

There are two limitations on what products are eligible for accelerated approval. First, the product must be used to treat a serious or life-threatening illness like cancer. Second, the drug must provide a meaningful therapeutic benefit compared to other available therapies. People often equate accelerated approval with reliance on a surrogate endpoint, which is defined as an endpoint that is reasonably likely to predict clinical benefit. While that is one pathway to accelerated approval, it is not the only one.

Avastin's accelerated approval for metastatic breast cancer was based on the other pathway, its effect on a clinical endpoint other than survival or irreversible morbidity. Here, as

you've heard from Dr. Pazdur, the clinical endpoint that was the basis for Avastin's metastatic breast cancer approval was a radiographic measurement called PFS.

Regardless of which pathway to accelerated approval is used, approval is granted on the condition that the applicant conduct additional studies to verify the product's clinical benefit. Dr. Pazdur explained how CDER scientists evaluate whether a product provides a clinical benefit.

The design of these post-approval studies, which are sometimes called confirmatory studies, is proposed by the sponsor and agreed to by CDER. The studies must be carried out with due diligence and they must be "adequate and well-controlled." Adequate and well-controlled is a term of art, but, in essence, it means that CDER's risk-benefit judgments must be based on data from rigorous clinical trials, not anecdotal information or unsubstantiated theories.

So I've taken you through the particulars of what the statute and the regulations say about

accelerated approval. However, it is vital to keep in mind the public health purpose of these provisions.

The accelerated approval framework embodies a delicate balance of two compelling and sometimes competing public health interests. The first is the public health interest in providing patients with access to promising new therapies as soon as possible. That's why, as I've described, the accelerated approval program permits approval based on data showing an effect on an endpoint other than survival, or irreversible morbidity, or a surrogate endpoint. The tradeoff for providing patients with earlier access to drugs, however, was and is uncertainty about whether a drug's clinical benefit will be verified in the post-approval studies.

Under this framework, it is entirely possible that, in some cases, clinical benefit will not be verified. In that case, patients would be exposed to a drug that does not provide a clinical benefit or for which the risks outweigh the benefits.

The second compelling public health interest embodied in the accelerated approval program, therefore, is to protect patients from such drugs. That is why the statute and regulations include a process for accelerated withdrawal as a safeguard against the risk that patients are exposed to a drug that does not provide a clinical benefit, or for which the risks outweigh the benefits.

So although the shorthand for the regulatory framework we'll be talking about today is accelerated approval, an integral part of it is accelerated withdrawal. It's a two-way street. The balance of approval and withdrawal are needed to make the program work, and thereby protect patients and the public health.

As you can see on this slide, the regulations authorize FDA to withdraw accelerated approval if, among other things, a post-approval study fails to verify the drug's clinical benefit, or other evidence demonstrates that the drug is not shown to be safe or effective. Either one is grounds for withdrawal.

As will be explained by CDER scientists, both of these criteria are met here. That means that the legal standard for withdrawal has been met. Thank you.

The next speaker will be Dr. Lee Pai-Scherf.

DR. PAI-SCHERF: Good morning. My name is Lee Pai-Scherf. I'm a medical officer in the Office of Oncology Drug Products, CDER, FDA. I will present CDER's review of the Avastin application for metastatic breast cancer.

This is CDER's Avastin review team. This slide shows the outline of my presentation, background information, accelerated approval of Avastin for metastatic breast cancer, studies AVF2119g and E2100, confirmatory studies AVADO and RIBBON 1, additional study metastatic breast cancer, RIBBON 2, summary, and conclusions.

Avastin has been in the United States market since February 2004. This slide shows the current approved indications for Avastin. Genentech's initial trials supporting the accelerated approval for Avastin for metastatic breast cancer consisted

of AVF2119g and E2100. 2119g was a randomized open-label trial of capecitabine with or without Avastin for second- and third-line metastatic breast cancer. It was intended to support the initial approval of Avastin. The study failed to meet its primary endpoint of progression-free survival.

The study enrolled 462 patients with progressive metastatic breast cancer, previously treated with anthracycline and taxane. Eligible patients were randomized to receive capecitabine alone or capecitabine with Avastin.

This slide shows the Kaplan-Meier progression-free survival curves for AVF2119g. There was no statistical improvement in PFS with the addition of Avastin to capecitabine. Overall survival was a secondary endpoint. There was no improvement in overall survival with the addition of Avastin to capecitabine.

In May 2002, Genentech identified E2100 as an additional study intended to support drug approval. The study was conducted by the Eastern

Cooperative Oncology Group and supported by the National Cancer Institute. E2100 was an open-label, randomized study of paclitaxel with or without Avastin for patients with HER2-negative, recurrent or metastatic breast cancer who had not received prior chemotherapy for their metastatic disease.

In May 2006, Genentech submitted an sBLA for first-line metastatic breast cancer based on the entering results of E2100. After review of the submission, CDER issued a filing deficiency letter. Key issues are listed on this slide. Subsequent to the filing deficiency letter, Genentech conducted a data clean-up and retrospectively collected radiographic scans to perform an independent blinded review of the progression events. In August 2007, Genentech resubmitted the sBLA.

The primary endpoint of the study was PFS, as determined by an independent radiographic review. Results are shown in this table. The addition of Avastin to paclitaxel resulted in a statistically significant improvement in PFS, with

a hazard ratio of 0.48. That is a 52 percent reduction in the risk of disease progression or death, compared to paclitaxel alone. The median PFS was 5.8 months for the paclitaxel arm and 11.3 months for the paclitaxel plus Avastin arm. Overall survival was a secondary endpoint. There was no significant difference in overall survival between the two treatment arms as shown here.

Quality of life was assessed using the trial outcome index from the FACT-B questionnaire. The primary analysis was to compare the changes in TOI score from baseline to week 17 for patients in each arm. Genentech claims that the addition of Avastin to paclitaxel treatment does not result in additional detriment to a patient's quality of life. CDER has concerns with this quality of life data. The open-label designed has a high potential for bias, there were significant missing data, and we have concerns regarding the imputation methods used in the analysis.

In summary, there is no data showing improvement in quality of life in the E2100 study.

The review team had several issues with the data submitted to support Avastin approval for metastatic breast cancer. There was only one single open-label study with positive data to support approval. While the PFS result was felt to be robust based on the sensitivity analysis conducted for PFS and supported by the objective response rate, there was no confidence on the magnitude of the reported PFS.

Factors affecting confidence in magnitude of PFS findings were, there were missing scans in 10 percent of the patients; 34 percent of the patients were not followed until an independent review determined a PFS event or end of study; lack of reliability in the determination of radiographic disease progression and the date of progression between the independent radiologist and study investigators; and there was no improvement in overall survival.

In addition, there was incomplete assessment of toxicity, 20 percent increase in grade 3 to 5 toxicities, with the addition of Avastin to

paclitaxel, and a 1.7 percent treatment-related death in the Avastin plus paclitaxel arm. In addition, the results of AVF2119g trial showed no improvement in progression-free survival or overall survival in the second- and third-line setting.

Results of E2100 were presented to ODAC in December 2007. ODAC members were asked the following question. Are the data provided sufficient to establish a favorable risk-benefit analysis for the use of bevacizumab plus paclitaxel for first-line treatment of patients with metastatic breast cancer. Five members voted no and four yes.

Summarized here, the ODAC members had a number of concerns, including concerns that E2100 study had shortcomings and inconsistencies, such as data collection and imaging discordance, concerns of the toxicity of Avastin and the fact that other agents are available in this setting. The committee was reaffirmed that if PFS is to be used, the study must be powered for survival to ensure that benefit outweighs the risks.

On February 2008, CDER granted accelerated approval to Avastin. This was a difficult decision for CDER. The magnitude of PFS effect suggested a clinical benefit, but needed further verification.

I will now present the results of AVADO and RIBBON 1. These two confirmatory studies were identified and proposed by Genentech and agreed to by CDER.

In November 2009, Genentech submitted AVADO and RIBBON 1 results, seeking to discharge its confirmatory study obligations and to expand the Avastin label to add the indications shown in this slide.

The AVADO study. The AVADO trial design is shown on this slide. Patients with metastatic breast cancer who had not received prior chemotherapy for metastatic breast cancer, HER2-negative, were randomized, 1 to 1 to 1, to receive docetaxel with placebo, or Avastin at 7.5 milligrams per kilogram, or 15 milligrams per kilogram.

Treatment continued until disease

progression or an acceptable toxicity. The protocol had a past study phase, which allowed for unblinded treatment for Avastin plus chemotherapy of choice of the investigator for patients who experienced disease progression. The study enrolled 736 patients in the three treatment arms.

Efficacy findings. The primary endpoint of this study is investigator-determined progression-free survival. The addition of Avastin to docetaxel resulted in a statistically significant but marginal improvement in PFS with a hazard ratio of 0.7 and 0.62 for the Avastin, 7.5 and 15 milligrams arm. The improvement in median PFS was less than one month. The median PFS was 7.8 months for the placebo arm, versus 8.7 months for the Avastin 7.5-milligram, and 8.8 months for the 15-milligram arm.

This slide shows the PFS Kaplan-Meier curves for the Avastin 7.5 versus placebo.

This next slide shows the PFS Kaplan-Meier curves for the Avastin, 15-milligram arm versus placebo.

Overall survival is a secondary endpoint in the AVADO trial. Genentech was required to collect and submit mature survival data, assessing whether the addition of Avastin to chemotherapy results in a deleterious effect on survival.

This slide shows the mature overall survival results of AVADO. There was no survival benefit with the addition of Avastin to docetaxel at either Avastin dose level. The median overall survival is 31.9 months for the placebo arm, 30.8 months, and 30.2 months for the Avastin-containing arms.

The hazard ratio was 1.1, favoring the placebo arm over the 7.5-milligram per-kilogram Avastin arm. This hazard ratio indicates that those patients in the Avastin arm on the study did not survive as long as those patients receiving docetaxel plus placebo, but this result was not statistically significant. Hazard ratio for the 15-milligram arm is 1.

Here is the overall survival Kaplan-Meier curves for Avastin 7.5 milligrams versus placebo, and the Kaplan-Meier survival curve for Avastin, 15

milligrams versus placebo.

Quality of life was assessed in the AVADO study using FACT-B questionnaire and Trial Outcome Index score. The primary analysis was to compare the FACT-B and TOI score changes from baseline to week 9, 15, and 30, 13. Genentech claims that the addition of Avastin to docetaxel did not negatively affect patients' quality of life. However, missing data and the imputation method used make this conclusion questionable. Therefore, there is no data showing improvement in quality of life in the AVADO study.

Safety. This slide shows the incidence of all adverse events, grade 3 to 5 adverse events, in serious adverse events for the AVADO study by treatment arm.

The AVADO study is one of the few studies, Avastin randomized controlled studies, that collected all adverse events on the study. As you can see, nearly 100 percent of the patients experienced at least one adverse event, fairly typical of this population.

The addition of Avastin to docetaxel leads to an increase in the incidence of grade 3 to 5 adverse events and serious adverse events as shown here. Serious adverse events are toxicities. They are serious or life-threatening, require medical intervention, hospitalization, or result in death.

The next two slides will show the incidence of clinically important adverse events, all grades, reported for the AVADO study. The toxicities listed here, bleeding hemorrhage, hypertension, proteinuria, wound healing complications, fistula gastrointestinal perforation are events known to occur with Avastin.

In the 15-milligram arm, bleeding hemorrhage was reported in more than 50 percent of the patients compared to 29 percent in the placebo arm. The majority of these events were grade 1 or 2. One in five patients, 22 percent, treated with Avastin, 15 milligrams, developed hypertension compared to 1 in 10 patients in the placebo arm.

Proteinuria was four times more frequent, wound healing complications, five times, fistula GI

perforation, three times more frequent in patients treated with Avastin, 15-milligram arm compared to the placebo arm. These toxicities were also increased, though to a lesser extent in the Avastin 7.5-milligram arm. In this AVADO trial, there were two deaths due to toxicities known to be associated with Avastin, one pulmonary hemorrhage and one gastrointestinal perforation.

Diarrhea, febrile neutropenia, hand-foot syndrome are toxicities known to be associated with docetaxel. They were also more frequent in patients treated with Avastin compared to docetaxel and placebo. Grade 3 and higher, clinically significant adverse events with more than 2 percent difference compared with placebo arm are shown in this slide. Febrile neutropenia, hypertension, fatigue, proteinuria are all significantly increased with the addition of Avastin to paclitaxel.

The following two slides summarize CDER's efficacy and safety findings for the AVADO trial. While the difference in PFS between the arms was

statistically significant with a hazard ratio of 0.7 and 0.62 for the Avastin arms, the magnitude of effect was marginal. The observed improvement in median PFS is less than 1 month.

There was an 18.7 difference in overall response rate with the addition of Avastin to docetaxel. There was no improvement in overall survival with the addition of Avastin to docetaxel. Hazard ratio of overall survival was 1.1 in the 15-milligram arm, favoring the placebo. And there's no data showing improvement in quality of life.

This marginal improvement in PFS, an 18 percent difference in response rate, comes at a toxicity cost. The addition of Avastin to docetaxel led to an increased incidence of serious adverse events, grade 3 to 5 events. The increase of adverse events is due to unique events attributable to Avastin, such as hypertension, proteinuria, wound healing complications, and other AEs.

Adverse events known to be associated with

docetaxel were also increased with the combination, and there were Avastin-related deaths. There was no improvement in survival with the hazard ratio favoring the placebo arm in the 7.5 milligram arm. And there's no data showing improvement in quality of life.

I will now move onto the second confirmatory trial, RIBBON 1. The RIBBON 1 trial design is shown in this slide. Briefly, patients with metastatic breast cancer who had not received prior chemotherapy for metastatic disease, HER2-negative, were randomized 2 to 1 to receive chemotherapy with Avastin or placebo. Chemotherapy choice were either anthracycline-based, taxane-based, or capecitabine. Choice of the chemotherapy was at the discretion of the investigator and was specified prior to randomization for use as a stratification variable.

The taxane/anthracycline cohort and capecitabine cohort were analyzed separately for comparisons of PFS within each subgroup. Treatment continued until disease progression or an

acceptable toxicity. And similar to AVADO, RIBBON 1 also allowed for open-label treatment with Avastin plus chemotherapy, of choice by the investigator for patients who experienced disease progression.

RIBBON 1 enrolled 1,237 patients. In the taxane/anthracycline cohort, 50 percent of the patients received taxane-based chemotherapy and 50 percent receive anthracycline-based chemotherapy.

Next, I will present CDER's findings for the taxane/anthracycline cohort. The primary efficacy endpoint of the study was investigator-determined PFS. Results are shown in this slide. The addition of Avastin to taxane/anthracycline resulted in a statistically significant improvement in median PFS of 1.2 months, with a hazard ratio of 0.64. The median PFS was 8 months for the placebo arm and 9.2 months for the Avastin-containing arm.

This slide shows the PFS Kaplan-Meier curves for the taxane/anthracycline cohort. Overall survival of taxane/anthracycline cohort is shown

here. As previously stated, overall survival is both an efficacy as well as a safety endpoint. There was no survival benefit with the addition of Avastin to taxane- or anthracycline-based chemotherapy.

Similar to AVADO trial, final survival data in this arm, in the RIBBON 1 trial, showed a hazard ratio of 1.1, favoring the placebo arm. Median survival was 27.5 months for the Avastin-containing arm, and median survival for the placebo arm was not yet reached at the time of the data cutoff.

Here are the overall survival Kaplan-Meier curves for taxane and anthracycline cohorts versus the placebo arm. As discussed earlier, accelerated approval was granted for Avastin plus paclitaxel, a taxane. As a result, prespecified overall survival subgroup analysis was conducted to take a closer look at the taxane subgroup highlighted here.

At the time of the data cutoff, there were numerically more deaths in the Avastin-containing arm than placebo arm, 50 percent versus 43 percent. The hazard ratio for the taxane subgroup was

26.4 months -- the hazard ratio for the taxane subgroup, sorry, was 1.24, strongly favoring the placebo arm. Median overall survival was26.4 months for the Avastin arm, and median survival for the control arm was not yet reached at the time of data cutoff. For the anthracycline subgroup, the number of deaths was similar and the hazard ratio was less than 1.

CDER acknowledges the exploratory nature of these analyses and the small sample size. With 45 events in the placebo arm, this finding must be interpreted with caution. The overall Kaplan-Meier survival curve for the taxane subgroup is shown here. The upper curve, in red, is the placebo arm, and the lower curve, in blue, is the Avastin arm.

As previously stated, the reason CDER is interested in this subgroup is because the accelerated approval was granted for Avastin plus paclitaxel and/or the taxane, based on the E2100 study.

We will move on to the safety findings for the taxane/anthracycline cohort of the RIBBON 1

study. This slide shows the safety overview. In contrast to the AVADO trial, RIBBON 1 collected only selected adverse events. In the taxane subgroup, there were 20 percent more adverse events in the Avastin-containing arm compared to placebo. Serious adverse events were 2 times higher in the Avastin arm.

As shown in the right-hand column, the addition of Avastin to anthracycline-based chemotherapy also led to an increase in incidence of all adverse events, serious adverse events, and grade 3 to 5 adverse events.

As shown here, and in the next two slides, the difference in incidence of adverse events leading to study drug discontinuation was significantly higher in the Avastin arm than in the placebo arm for both the taxane and anthracycline-based chemotherapy subgroups. In the taxane and Avastin subgroup, 24 percent of the patients, 1 in 4, discontinued Avastin due to an adverse event.

Common adverse events leading to drug discontinuation are listed here: gastrointestinal

perforation and fistula, hypertension, left ventricular dysfunction, proteinuria, and hemorrhage.

In the anthracycline plus Avastin subgroup of RIBBON 1, 15 percent of the patients discontinued Avastin due to an adverse event. Adverse events leading to drug discontinuation were left ventricular dysfunction, myocardial infarction, hypertension, wound dehiscence, and proteinuria.

This table shows grades 3 and higher adverse events, with more than 2 percent difference compared to the placebo arm for the taxane and anthracycline subgroup. Hypertension, febrile neutropenia, bleeding hemorrhage, proteinuria, and left ventricular systolic dysfunction were all occurring at a much higher incidence in the Avastin-containing arm than in the control arm.

Grade 3 or higher hypertension was 5 times and 10 times more frequent with Avastin than the control arm. In the taxane subgroup, grade 3 and higher hemorrhage was 5 times more frequent.

Grade 3 and higher proteinuria was 4 times, and 2 times more frequent in the Avastin arms compared to the control arm.

There were four deaths due to gastrointestinal perforation and one due to pulmonary hemorrhage. These are known adverse events, related toxicities. These are Avastin-related toxicities.

The following slides summarize CDER's efficacy and safety findings for the taxane/anthracycline cohort. The study met its primary improvement in PFS, with a hazard ratio of 0.64. However, the magnitude effect is marginal. The observed improvement in median PFS is 1.2 months. There was a 13.3 difference in overall response rate. There was no improvement in overall survival, with a hazard ratio of 1.1 for the entire cohort and 1.25 for the taxane subgroup, strongly favoring the placebo arm.

The marginal improvement in PFS and tumor shrinkage comes at a toxicity cost. There was an increased incidence of serious adverse events and

grades 3 to 5 adverse events. The increase in adverse events is due to unique events attributable to Avastin. One in 4 patients discontinue Avastin due to toxicity in the taxane subgroup, and there were deaths related to toxicities, known to be associated with Avastin. There was no improvement in overall survival, with a hazard ratio favoring the placebo arm, 1.25 for the taxane subgroup. And no quality of life data were collected in this study.

Next, the capecitabine cohort for the RIBBON 1 trial. This slide shows the progression-free survival result of the capecitabine cohort. The addition of Avastin to capecitabine resulted in a statistically significant improvement in median PFS of 2.9 months, with a hazard ratio of 0.69. The median PFS was 5.7 months for the placebo arm and 8.6 months for the capecitabine plus Avastin arm.

Here are the PFS Kaplan-Meier curves for the capecitabine cohort. There was no improvement in overall survival with the addition of Avastin to

capecitabine. Median overall survival was 22.8 months for the placebo arm and 25.7 months for the capecitabine and Avastin arm, with a hazard ratio of 0.88, not statistically significant, but favors the Avastin-containing arm.

This slide shows the overall survival Kaplan-Meier curve for the capecitabine cohort. This next slide shows the safety overview for the capecitabine cohort. There was a 13 percent increase in the incidence of any adverse events that were collected in grade 3 to 5 adverse events with the addition of Avastin to capecitabine. Serious adverse events were minimally increased 5 percent, and there was no difference in the incident of Avastin or placebo discontinuation between the two arms in this cohort.

This slide focuses on the grade 3 to 5 adverse events in the capecitabine cohort. They are significantly increased in the Avastin arm. Grade 3 and higher hypertension, proteinuria, arterial thromboembolic event, left ventricular systolic dysfunction, and wound dehiscence occurred

at a higher incidence in the Avastin-containing arm. Grade 3 to 4 hypertension was 10 times more frequent in the Avastin arm.

In addition, there was an increased incidence of cardiac events leading to death in the Avastin-containing arm, 2 deaths due to myocardial infarction, 2 due to cardiogenic shock and failure, and 1 cardiac arrest. There were no deaths related to cardiac events reported for the placebo arm.

This slide summarizes the findings for the capecitabine cohort. The study met its primary endpoint of improvement in PFS, with a hazard ratio of 0.69. The observed improvement in median PFS is 2.9 months. There was an 11.8 percent difference in overall response rate, and there was no statistical improvement in overall survival. The hazard ratio for survival was 0.88, favoring the Avastin arm.

The addition of Avastin to capecitabine also led to an increase incidence of serious adverse events and grade 3 to 5 events. Cardiac deaths, deaths due to cardiac events, occurred in five

patients in the Avastin arm.

Results of AVADO and RIBBON 1 were presented to ODAC in July 2010. Committee members were asked if the addition of Avastin to docetaxel in the AVADO study, and to taxane/anthracycline and capecitabine for RIBBON 1 study, represent a favorable risk-benefit analysis for the initial treatment of patients with metastatic breast cancer.

The committee was near unanimous in their vote, indicating that the addition of Avastin to these chemotherapy agents did not represent a favorable risk-benefit analysis for this indication. The committee was unanimous in their vote, concluding that the AVADO and RIBBON 1 results did not provide confirmatory evidence of clinical benefit of Avastin in combination with paclitaxel in this population. And the committee was near unanimous in recommending that the indication for treatment of metastatic breast cancer be removed from the Avastin label.

Shortly before the 2010 ODAC meeting,

Genentech submitted results of another study of Avastin for metastatic breast cancer, RIBBON 2. On the basis of RIBBON 2, Genentech again proposed to expand its indication for Avastin. Genentech requested Avastin label expansion for patients with metastatic breast cancer who have received prior chemotherapy to use Avastin in combination with taxane, capecitabine, and gemcitabine.

RIBBON 2 was a randomized placebo-controlled study of chemotherapy in combination with Avastin or placebo. Allowable chemotherapy agents, at the discretion of the investigators, were taxane, gemcitabine, vinorelbine, and capecitabine.

The study met its primary endpoint of improvement in PFS, with a hazard ratio of 0.78. The median PFS was 5.1 months for the placebo arm and 7.2 months for the Avastin arm. The difference in median PFS was 2.1 months. There was no survival benefit with the addition of Avastin to chemotherapy for this population.

Key efficacy results of the five randomized control studies in metastatic breast cancer, three

studies for first-line metastatic breast cancer, and two studies for second- and third-line metastatic breast cancer are summarized in this table. The shaded column lists the results of PFS, hazard ratio, and difference in median PFS. With the exception of E2100, the hazard ratio ranged from 0.62 to 0.98 with median difference in PFS from 0.7 to 2.9 months.

These findings are all statistically significant. However, statistically significant is not the same as clinical benefit. None of these trials, including E2100, showed an improvement in overall survival. The hazard ratio for overall survival is more than 1 in the AVADO 7.5-milligram arm and the taxane/anthracycline cohort in RIBBON 1 trial, favoring the placebo arm.

Overall response was a secondary endpoint. Tumor shrinkage ranged from 10 to 27 percent in the trials, as shown here in this table. Since this population was generally asymptomatic or minimally symptomatic at the time of the study entry, the higher response rate with Avastin provides evidence

of activity but not of clinical benefit. There is no data showing improvement in health-related quality of life in any of these trials.

The addition of Avastin to chemotherapy resulted in an overall increase in serious adverse events and grade 3 to 5 adverse events. As I noted earlier, serious adverse events are toxicities. They are serious or life-threatening, require medical intervention, hospitalization, or result in death.

Note that all patients were either asymptomatic or minimally symptomatic at the time of the study entry. When metastatic disease in a patient is not symptomatic, the delay in time to progression accompanied by treatment-related toxicity may not increase the patient's quality of life. On the contrary, the most common toxicity of Avastin is grade 1 to 2 bleeding, reported in more than 50 percent of the patients, in hypertension, which can occur in 1 out of 5 patients receiving Avastin. Grade 3 and higher hypertension was nearly 10 times more frequent in patients receiving

Avastin.

Other serious adverse events such as hemorrhage, gastrointestinal perforation, fistulas, arterial and venous thromboembolic events, proteinuria, wound healing complications, left ventricular dysfunction, neutropenia, and febrile neutropenia are all events associated with Avastin. They are not as common as grade 1 to 2 hypertension and epistaxis, but they certainly do not improve many patients' quality of life.

The toxicities observed in these trials are well-known to Avastin, and the current Avastin label carries a box warning for gastrointestinal perforation, wound healing complications, and hemorrhage. These toxicities are severe and sometimes fatal.

In conclusion, the totality of data does not demonstrate a favorable risk-benefit evaluation for the continued marketing of Avastin for metastatic breast cancer.

Confirmatory studies, AVADO and RIBBON 1, failed to verify clinical benefit in patients with

metastatic breast cancer. They failed to substantiate the magnitude of PFS in E2100. They failed to show any improvement in overall survival. And there's no data showing improvement in health-related quality of life.

Avastin, in combination with chemotherapy has a modest effect on PFS, balanced against its risks of serious and life-threatening toxicities. Thank you.

The next speaker is Dr. Patricia Keegan.

DR. KEEGAN: Good morning. My presentation focuses on CDER's assessment of Genentech's arguments, why the metastatic breast cancer indication for Avastin should be maintained while Genentech conducts an additional study to attempt to substantiate the magnitude of the treatment effect on progression-free survival observed in the E2100 study.

Genentech has argued in this proceeding that FDA should maintain approval for Avastin while additional research is conducted. Genentech's specific arguments are that FDA should maintain

approval while Genentech conducts and designs new confirmatory trials; that Genentech's completed confirmatory trials met their primary endpoint, but CDER changed the approval standard; that despite the results of the completed confirmatory trials, the proposed new trial is likely to substantiate the results of E2100 because the efficacy of Avastin depends on the chemotherapy partner and the duration of combination therapy, and that CDER has overstated the safety risks of Avastin.

CDER has considered Genentech's arguments, and CDER's responses are that CDER has consistently communicated that the magnitude of the progression-free survival effect is critical, that the E2100 results are not representative of Avastin's true treatment effect. That is, the E2100 results are an outlier.

I note that Genentech has not provided evidence that Avastin's efficacy depends on the chemotherapy partner or the duration of the combination of Avastin and chemotherapy. In addition, a recently completed phase 2 trial

assessing the safety and activity of Avastin, in combination with paclitaxel, does not substantiate the E2100 results.

The Genentech's proposed confirmatory study is years from completion, and current data suggests that this new trial is unlikely to substantiate clinical benefit, and CDER has not overstated the risks of Avastin. When Avastin is used for the treatment of metastatic breast cancer, these risks outweigh the limited benefits, the limited treatment effects.

I will begin by describing the manner in which CDER has consistently communicated to Genentech that the magnitude of the progression-free survival effect is a critical aspect, upon which CDER would base a decision as to whether clinical benefit had been demonstrated.

CDER's approval standards and regulatory decisions are based -- and have been consistent throughout its review of Avastin's metastatic breast cancer application, and have been communicated to Genentech specifically. CDER

communicated to Genentech on several occasions that the magnitude of the treatment effect on progression-free survival was critical to determining whether this constituted clinical benefit, including on October 28th, 2004, December 5th, 2007, and on February 22nd, 2008. To be clear, CDER did not advise Genentech that any effect on progression-free survival, regardless of its magnitude, would be sufficient to demonstrate clinical benefit.

In addition, this general policy is clearly stated in FDA's May 2007 guidance for industry on clinical trial endpoints for the approval of cancer drugs and biologics. This guidance states that whether an improvement in progression-free survival represents a direct clinical benefit or a surrogate for a clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies.

On December 5th, 2007, during the ODAC meeting, Genentech's own consultant, Dr. Eric Winer, listed similar criteria for determining that

an effect on progression-free survival is clinical benefit. He stated, for progression-free survival to equal benefit, for it to be meaningful, this progression-free survival needs to be substantial in magnitude. It needs to be established with confidence. And ideally, it should be supported by other measures of efficacy, by survival, by quality of life, and by objective response rate.

Genentech asserts that CDER was already informed of the difference in progression-free survival from the AVADO study, prior to granting accelerated approval to Avastin in first-line metastatic breast cancer, accepting that the totality of the data reasonably predicted the likelihood of clinical benefit. Thus, according to Genentech, CDER is now changing the approval standards. This is not accurate.

CDER communicated that there are three acceptable ways to confirm benefit, this seen in E2100. And these were to substantiate the magnitude of the E2100 progression-free survival result, or to demonstrate an improvement in overall

survival, or to demonstrate an improvement in health-related quality of life.

When CDER requested the top-line AVADO results, the purpose was to confirm that the AVADO study had met its primary endpoint and to provide evidence that AVADO was not a failed trial, as was the case for the AVF2119g.

CDER acknowledges that the progression-free survival effect observed in the AVADO study is small. However, Genentech also directed CDER to the promising trend in overall survival in the top-line results. CDER notes that the AVADO trial could have confirmed clinical benefit if the effect on overall survival had been demonstrated.

This slide is taken from Genentech's submission of February 2008, describing the top-line results of the AVADO trial. The PowerPoint presentation included a preliminary analysis of overall survival.

I direct your attention to the area circled in red on this slide, as provided by Genentech, which shows a positive trend in overall survival

for the Avastin 15-milligram per-kilogram arm compared to docetaxel alone, with an hazard ratio of 0.65 and an unadjusted p value of 0.594.

As Dr. Pazdur noted, improvement in survival is the gold standard for any oncology drug. Unfortunately, as you have already seen, from Dr. Pai-Scherf's presentation, the mature analysis of the AVADO results demonstrated no effect on overall survival, with a hazard ratio of 1.1.

Finally, CDER considered the totality of the data. The top-line results of the RIBBON 1 study, which were not submitted by Genentech prior to the accelerated approval action, also showed a smaller effect on progression-free survival than E2100 and no effect on overall survival.

Genentech asserts that CDER should use hazard ratios, but not median progression-free survival times, to characterize effect sizes. However, characterization of effect sizes by the use of hazard ratios, which assess the treatment effects relative to the control arm across the entire period of the study, and median time to

event values, which provide a temporal context for judging the clinical relevance of the hazard ratio, is an accepted convention in describing clinical study results for time-to-event comparisons. Genentech's current position is inconsistent with its own past practices and advertising claims.

At the request of CDER, Genentech voluntarily agreed to suspend advertising for the metastatic breast cancer indication. Prior to that point, the characterization of the treatment effect in the E2100 study was described by Genentech using median progression-free survival times for each arm. This was clearly a major component of the advertising claims, as can be seen from these graphics on the slide taken from a Genentech ad for Avastin.

I will now discuss the information which led to CDER's conclusion that the results of the E2100 study are not representative of the true treatment effects of Avastin in metastatic breast cancer and why CDER considered the E2100 results on progression-free survival to be an outlier.

The requested indication for Avastin, for treatment of metastatic breast cancer, was first considered in a supplement containing the results of one failed trial, AVF2119g, and one positive trial, E2100. CDER therefore required more data to understand how to reconcile that inconsistency.

The totality of the data from five adequate and well-controlled trials involving seven independently powered comparisons show that the results seen in the E2100 trial are not representative of the Avastin treatment effect in metastatic breast cancer.

This slide contains a bar graph displaying the absolute difference in median progression-free survival times across the seven independently powered comparisons in controlled trials submitted by Genentech. The graph clearly shows that the absolute difference in progression-free survival time in E2100, the red bar, is not representative of that seen across the other six comparisons in first- and second-line treatment of metastatic breast cancer.

Genentech acknowledges these differences in effect size across studies and poses two hypotheses to explain the failure to confirm the magnitude of the progression-free survival effect in six additional comparisons.

However, Genentech's hypotheses are not supported by data. Additionally, there is new information from a randomized phase 2 trial conducted by the Cancer International Research Group, which I will refer to as Study 10, that does not substantiate the magnitude of the treatment effect observed in the E2100 trial.

Genentech has stated multiple hypotheses can be generated for why a differential effect would be observed with distinct chemotherapy partners. However, their lead hypotheses are that different chemotherapy partners substantially alter Avastin treatment effect and that the duration of combination therapy substantially alters Avastin treatment effect.

No convincing or persuasive evidence has been provided to support either of these

hypotheses. Genentech's evidence appears to consist only of the observation of smaller effect sizes in AVADO and RIBBON 1. However, associations do not demonstrate causality. Classic pharmacokinetic study designs have been developed to test such hypotheses, but these tests have not been done, or if performed, have not been submitted to CDER.

Before we can reasonably conclude that the chemotherapy partner is an important factor, Genentech should provide data to support this. However, CDER is unaware of and Genentech has not provided this type of scientific data, such as evidence of synergism between Avastin and paclitaxel. By synergism, I mean that the treatment effects of Avastin and paclitaxel given together is larger than the sum of the treatment effects of each drug when that drug is given alone.

In addition, we have not been provided with evidence of pharmacokinetic interactions between Avastin and any of the chemotherapeutic agents used in AVADO or RIBBON 1, nor have we been provided

with evidence of antagonism between Avastin and any of the chemotherapeutic agents administered in AVADO or RIBBON 1. By antagonism, I mean that the treatment effects of Avastin plus other chemotherapeutic agents, when given in combination, are smaller than the sum of the treatment effects when each drug is given alone.

To the contrary, the available pharmacokinetic data indicate that there are no interactions between Avastin and any of the chemotherapeutic agents administered with Avastin in the AVADO and the RIBBON 1 studies.

Genentech's theory is that limitations on the duration of combined administration of Avastin and chemotherapy altered the treatment effect. This is inconsistent with the results of other studies of Avastin. Specifically, there is limited treatment effects observed when Avastin was given in combination with taxanes or capecitabine in RIBBON 1, where there were no restrictions on the number of cycles of chemotherapy treatment.

In addition, improved survival and confirmed

progression-free survival effects were demonstrated in colorectal cancer, lung cancer, and renal cell cancer, where duration of chemotherapy, and thus combination therapy, was limited to a specific number of cycles per treatment period. Genentech has not conducted and does not propose to conduct a study to test this hypothesis.

Genentech has identified several studies, purporting to confirm the duration of progression-free survival observed in E2100. CDER's response is that these studies cannot confirm the magnitude of the PFS effect because the data were obtained in single-arm trials, or randomized trials with comparisons to investigational controls, or in small controlled studies with imprecise estimates of the effect size.

There is new evidence that supports CDER's conclusion that the E2100 result is an outlier. The new evidence which CDER refers to is Study 10, cited by Genentech as new evidence supporting the E2100 results. Study 10 is a three-arm, randomized, placebo and active-controlled trial,

activity-estimating trial, that was published in the Lancet in April 2011.

Study 10 accrued 2082 patients, receiving first-line treatment for HER2-negative metastatic breast cancer between December 2006 and July 2008. Patients were allocated equally to one of three treatment arms, consisting of paclitaxel in combination with a placebo tablet for motesanib, paclitaxel in combination with motesanib, or paclitaxel in combination with Avastin, at the same doses and schedules as employed in the E2100 trial. The primary endpoint of Study 10 was overall response rate.

In the pairwise comparison of the Avastin-containing arm to the paclitaxel-alone arm, the hazard ratio for progression-free survival was 0.79, with a median progression-free survival of 11.5 months in the Avastin-containing arm, and 9 months for the paclitaxel-alone arm, a difference of 2.5 months. The overall response rate for the Avastin-containing arm was 52 percent, as compared to 41 percent with paclitaxel alone. None of these

differences were significant.

The results for E2100 and Study 10 are presented for comparison in this table. The difference in median progression-free survival times is only 2.5 months, similar to the results of AVADO and RIBBON 1, and smaller than that observed in the E2100 trial. The hazard ratio for Study 10 is 0.79, and the lower bound of the confidence interval excludes the observed hazard ratio for progression-free survival in the E2100 trial of 0.48.

The magnitude of the treatment effect of Avastin on overall response rate, the primary endpoint of this study, was only 11 percent, again, similar to that observed with AVADO and RIBBON 1, and smaller than that reported for the E2100 trial.

While cross-study comparisons should be reviewed with caution, I note that one difference between E2100 and Study 10 are the treatment effects in the control arm of each trial, treated with the same dose and schedule of paclitaxel.

For example, the median progression-free

survival time for the control arm in E2100 was 5.8 months, whereas it was 9 months in Study 10. Similarly, the overall response rate for the control arm in the E2100 study was 22.2 percent, whereas it was 41 percent for the control arm in Study 10.

This bar graph for between-arm differences for progression-free survival has been updated to include the results of Study 10. The results of Study 10 suggest that an additional study, using the same dose and schedule of Avastin and paclitaxel, as in E2100, is unlikely to substantiate the magnitude of the progression-free survival treatment effect seen in the E2100 study.

I will now discuss why, based on the totality of the data, the indication for Avastin for metastatic breast cancer should be withdrawn, pending the completion of studies which are successful in confirming clinical benefit.

Based on its hypotheses that effectiveness of Avastin depend on the chemotherapy partner and the duration of combination treatment, Genentech

proposes to conduct a fourth trial in the first-line treatment of metastatic breast cancer to attempt to substantiate the magnitude of Avastin's treatment effect observed in the E2100 trial.

With the exception of the use of a placebo infusion in the control arm, the proposed treatment plan is the same as that used in the E2100 trial. The proposed trial differs from the E2100 trial in three aspects. First, it is a double-blind design rather than an open-label trial. Second, the randomization will be stratified by high versus low serum VEGF-A levels. Third, the trial has two co-primary endpoints. They are to assess the treatment effect of Avastin on progression-free survival in the overall population and to assess the treatment effect of Avastin on progression-free survival in the subset of women with high VEGF-A serum levels.

There are several factors which may delay timely completion of this trial. First, the protocol is under development. Second, the proposed study, which by its design requires

co-development of a validated biomarker assay for accurate and reliable measurement of serum VEGF-A levels that will be used to identify a subpopulation of women with metastatic breast cancer, who might benefit from the addition of Avastin to standard chemotherapy, remains under development. Third, based on recently completed studies, submission of trial results are projected to be three or more years from enrollment of the first subject until submission.

Finally, I will discuss why CDER has not overstated the risks of Avastin and why, in the setting of metastatic breast cancer, these risks outweigh the limited treatment effects demonstrated across multiple randomized clinical trials.

Genentech argues that FDA has overstated the risk profile of Avastin in metastatic breast cancer through use of general terms, for example, substantial, rather than specific incidence values in the December 16th office director decisional memo. Genentech also states that common adverse events associated with Avastin are clinically

manageable and the more serious effects are not common and are clearly set forth in the prescribing information.

CDER agrees that in other approved indications with confirmed clinical benefit, such as improved survival or substantiated clinically important increases in progression-free survival, the risks of Avastin are acceptable. However, the limited effects on progression-free survival and overall response rate in metastatic breast cancer do not outweigh the serious and potentially fatal risks, for example, hemorrhage and gastrointestinal perforation, nor the ongoing risks of new, or worsening hypertension, or renal injury manifesting as proteinuria.

As I begin my discussion of the risks of Avastin, I wish to remind the committee and Dr. Midthun that most of the adverse reaction data described in the Avastin product label is limited to severe, life-threatening, serious, or fatal toxicities, specifically NCI CTCAE grade 3 to 5 non-hematologic toxicity, and NCI CTCAE grade 4 to

5 hematologic toxicity for studies supporting approvals in metastatic breast cancer, second-line metastatic colorectal cancer, non-small cell lung cancer, and for more than half the patients enrolled in the studies supporting the approval for the first-line metastatic colorectal cancer indication.

CDER agrees that the information in the product labeling is accurate and that the product labeling clearly describes that Avastin causes serious, irreversible, and life-threatening toxicities. CDER has not overstated these risks.

In addition to these serious and potentially fatal, life-threatening risks, there are more common toxicities of Avastin, which include minor bleeding, most frequently manifesting as epistaxis, hypertension, proteinuria, and an increased risk of chemotherapy-related toxicities such as neutropenia, febrile neutropenia, sensory neuropathy, diarrhea, and hand-foot syndrome.

The clinical impact of the more common Avastin toxicities may be underestimated by

oncologists because they are novel, and the initial presentation is clinically asymptomatic. However, lack of symptoms should not be equated with lack of risk. These risks are all the more important in a patient population receiving initial treatment for metastatic breast cancer, where more than half are expected to live more than two years.

CDER has received little information on reversibility of these toxicities and no data on the need for additional medication and clinic visits to monitoring and treat patients with these effects, or the impact of Avastin-induced toxicities of hypertension and renal injury on the ability to receive or tolerate second-line or subsequent therapies.

I will spend a few minutes discussing what we know and what we do not know about these toxicities.

The description of the incidence and severity of proteinuria in product labeling is limited by the type and extent of safety data collected in clinical trials. The labeled findings

are similar to the more comprehensive risk analysis conducted by Wu and colleagues and published in the Journal of the American Society of Nephrology.

In this meta-analysis, the incidence of renal injury manifesting as proteinuria across five randomized clinical trials is 13.3 percent, or 1 in 8 patients treated. This corresponds to a 2.8-fold increase in the risk of developing proteinuria. The incidence of severe or life-threatening proteinuria in randomized clinical studies is 2.2 percent, or 1 in 50 patients treated. This corresponds to a 4.8-fold increase in the risk of developing severe or life-threatening proteinuria.

The clinical course and outcomes of proteinuria were not collected in most clinical studies submitted by Genentech, and therefore the consequences of Avastin-induced renal toxicity remain poorly characterized. CDER is awaiting the submission of the final report and primary data from the postmarketing sub-study to NSABP CO8, intended to further characterize these risks.

Data characterizing the clinical course of

proteinuria that are contained in the product label note that the median time to resolution of proteinuria was 6.1 months, and in patients with metastatic renal cancer with a median follow-up of 11.2 months, proteinuria had not resolved in 40 percent of the patients.

Pathologic findings, specifically thrombotic microangiopathy, has been identified in renal biopsy specimens obtained from patients with only NCI CTC grade 1 or 2 proteinuria.

The following table was abstracted from an article by Izzedine in the European Journal of Cancer. The table provides characteristics of a series of 16 patients who developed proteinuria secondary to VEGF inhibitors, predominately Avastin therapy, where there was pathological evidence of thrombotic microangiopathy and renal biopsy.

I draw your attention to the middle columns in the expanded field, which lists the NCI CTCAE severity grade for each of these patients. Approximately half the patients in this series with pathologic evidence of thrombotic microangiopathy

were identified as having only NCI CTC grade 1 or 2 renal toxicity. This finding raises concerns that the NCI CTCAE severity grade may be a poor predictor of the severity of VEGF inhibitor-induced renal injury.

As I present the information on the risks of hypertension, please keep in mind that the criteria for mild and moderate hypertension in the NCI CTCAE versions 2 and 3 are inconsistent with practice guidelines for the treatment of hypertension, and thus are likely to underestimate the clinical severity.

The characterization of Avastin-induced hypertension described in the product labeling is based on the limited data, as I've already alluded to. The labeled findings are similar to the more comprehensive risk analysis conducted by Rampura and colleagues and published in the American Journal of Hypertension.

In this meta-analysis, the incidence of hypertension is 23.6 percent, or 1 in 4 patients treated. The incidence of severe or life-

threatening hypertension is 7.9 percent, or 1 in 13 patients treated. This corresponds to a 5.3-fold increase in the risk of developing severe or life-threatening hypertension.

While data were captured in clinical studies on the incidence of Avastin-induced hypertension, information on the clinical course and outcomes remains poorly characterized. CDER is again awaiting the submission of a postmarketing sub-study to NSABP CO8, intended to further characterize these risks.

In addition to the common toxicities, Avastin causes serious toxicities requiring major and minor surgery, hospitalization, persistent morbidity, and even death. CDER has not overstated the seriousness of these toxicities and acknowledges that they occur in less than 2 percent of patients as individual events, occurring at incidences ranging from 1 in 70 to 1 in a thousand patients. These less common but serious toxicities are fistula formation, gastrointestinal perforation, hemorrhage requiring transfusion or

other medical intervention, and impaired wound healing and death.

This morning we have heard from patients and their families describing how they feel they have benefited from Avastin. However, there are other voices that need to be heard. Those voices include a 53-year-old woman with metastatic breast cancer who suffered severe abdominal pain caused by gastrointestinal perforation that led to her death after 4 doses of Avastin; or an asymptomatic 33-year-old woman with treatment-naive metastatic breast cancer who suffered a massive fatal pulmonary hemorrhage after 11 doses of Avastin.

Given the limited treatment effects consistently demonstrated across multiple clinical trials and the unfavorable risk-benefit analysis, it is inappropriate to maintain the metastatic breast cancer indication for Avastin while Genentech plans to initiate new studies.

The treatment effects of Avastin in metastatic breast cancer are limited to a modest improvement in median progression-free survival and

a modest improvement in overall response rate among patients who receive Avastin and chemotherapy compared to chemotherapy alone. There was no evidence of an improvement in or relief from disease-related symptoms. There is no evidence of an improvement in overall survival. And all patients are exposed to the common risks of Avastin as well as the less common but life-threatening risks of Avastin.

Because of the confusion on this issue, I want to emphasize one point. Despite the hopes of everyone inside and outside this room, after conducting three trials enrolling more than 2,400 women receiving first-line treatment for metastatic breast cancer, there is no evidence that Avastin saves or extends lives.

As can be seen in this survival curve provided by Genentech, pooling the data across the three first-line trials in metastatic breast cancer, women in general who received Avastin as an add-on to standard chemotherapy did not live any longer than women in general who only received

standard chemotherapy.

The totality of the data suggests that Genentech's proposed study is not likely to confirm clinical benefit. Genentech may conduct further studies to attempt to show that Avastin provides a benefit for a subset of patients with metastatic breast cancer with high serum VEGF-A levels, but it is not appropriate for the product label for Avastin to contain claims which suggest that Avastin is safe and effective for treatment of women with metastatic breast cancer.

I will now turn over to Dr. John Jenkins.

DR. JENKINS: Good morning. I'm Dr. John Jenkins. I'm the director of the Office of New Drugs in the Center for Drug Evaluation and Research. I will now summarize and conclude CDER's formal presentation.

As you have heard, CDER's decision in 2008 to grant accelerated approval for Avastin for the first-line treatment of metastatic breast cancer was an extremely challenging one. At that time, the only data supporting approval came from a

single positive trial, E2100, which showed a promising effect on progression-free survival, or PFS, but not on overall survival or quality of life. In contrast, a second trial available at that time failed on all three endpoints.

These data were reviewed by ODAC in December 2007, and following a vigorous debate, the members narrowly voted against approval 5 to 4. After carefully considering ODAC's advice and the available data, CDER concluded that accelerated approval should be granted on the basis of the PFS finding from E2100 which, if confirmed by subsequent trials, was felt to result in a positive benefit-risk assessment for Avastin.

The approval was conditioned on the requirement that Genentech conduct additional postmarketing trials to confirm clinical benefit of Avastin in breast cancer. CDER's decision to allow Genentech to market this promising new treatment while additional trials were completed is consistent with the principles that underlie the accelerated approval program.

Assuming no change in the risk profile of Avastin, confirmation of clinical benefit could have been shown by demonstration of an effect on PFS similar in magnitude to that seen in E2100, demonstration of an improvement in overall survival, which is the gold standard for cancer drug approval, or demonstration of an improvement in quality of life such as symptoms, which patients value even in the fact of no improvement in overall survival. Unfortunately, none of the postmarketing trials have confirmed any of these clinical benefits.

Genentech has now submitted the results of five completed clinical trials of Avastin in patients with breast cancer, and the facts are the following.

First, no trial on its own, or the combined results of the five trials, has shown an improvement in overall survival. In other words, no trial has shown that patients treated with Avastin lived longer than patients not treated with Avastin.

Second, no post-approval trial has shown an improvement in PFS of the magnitude seen in E2100.

Finally, no trial has shown an improvement in health-related quality of life. In other words, no trial has shown that patients treated with Avastin feel better than patients not treated with Avastin.

The totality of the data available today strongly suggests that the PFS results seen in E2100 were an overestimate of the true effect of Avastin on PFS, and the true effect appears to be much smaller than that predicted at the time of accelerated approval. The small effect of Avastin on PFS must be considered in light of the serious and often poorly-tolerated and potentially lethal toxicity of the drug.

After carefully considering the totality of the available data, CDER now concludes that the modest effects of Avastin on PFS do not outweigh its risk in the treatment of breast cancer, and the indication should be withdrawn. Our decision is supported by ODAC's recommendation from the

July 2010 meeting, in which the committee voted 12 to 1 in favor of withdrawing the indication.

Genentech now argues that the agency should maintain the breast cancer indication for Avastin while the company designs and conducts an additional trial, or trials, in another attempt to confirm clinical benefit in this disease. The study that Genentech has proposed is essentially a repeat of the E2100 trial, a comparison of Avastin plus paclitaxel to paclitaxel alone.

A sponsor independent of Genentech recently completed such a trial, which Dr. Keegan referred to as Study 10. Study 10 was a phase 2 trial that enrolled approximately 300 patients with HER2-negative metastatic breast cancer. The magnitude of improvement in PFS in Study 10 was less than half of that seen in E2100. The results of Study 10 are in line with the results of the post-approval trials submitted by Genentech and provide support to CDER's conclusion that the PFS results from E2100 were an overestimate of the true effect of Avastin.

When we approved Avastin for breast cancer, we understood that the indication would be subject to the accelerated withdrawal procedures if clinical benefit was not confirmed. Accelerated withdrawal is a fundamental part of the accelerated approval pathway and serves as a backstop to protect the public from continued marketing of a drug if clinical benefit is not confirmed.

Under the accelerated approval regulations, FDA may withdraw an indication if the postmarketing clinical trials fail to confirm clinical benefit or if the evidence demonstrate that the product has not been shown to be safe and effective for the indication. In the case of Avastin for metastatic breast cancer, we conclude that both of these conditions have been met.

Genentech was aware of the accelerated withdrawal standards when CDER approved the breast cancer indication for Avastin in 2008. Now, three years later, they propose that withdrawal of accelerated approval is appropriate only under a new standard, which is shown on this slide. They

now propose that withdrawal is only appropriate when, “There is no reasonable likelihood of clinical benefit and no possibility that additional study might further characterize any existing benefit.”

This unprecedented interpretation of the accelerated withdrawal standards would turn the accelerated approval program on its head, allowing protracted marketing of drugs that have not been shown to be safe and effective while sponsors take numerous bites at the apple in an effort to confirm clinical benefit.

Such a standard could seriously undermine the integrity of the accelerated approval program. And it is very important that we preserve the integrity of the accelerated approval program, which has been very successfully used in oncology and other disease areas to provide early access to promising new therapies.

Forty-nine indications for cancer drugs have been approved under the accelerated approval program since 1995, and clinical benefit has been

confirmed for a majority of those drugs. In other cases, when post-approval trials failed to confirm clinical benefit or could not be completed in a timely manner, sponsors have voluntarily withdrawn their oncology drugs or indications.

Failure to confirm clinical benefit for a drug approved under accelerated approval, as occurred in the case of Avastin, is not an indication of a failure of the approval pathway. Rather, it is evidence that CDER is striking the right balance in making promising drugs available to patients while ensuring confirmation of clinical benefit following approval.

To maintain the integrity of this approval pathway, CDER must be able to use the accelerated withdrawal procedures when confirmatory trials fail to confirm clinical benefit. We cannot permit sponsors to evergreen approval of a drug that has not been shown to be safe and effective.

As I described earlier, the decision to grant accelerated approval for Avastin in the treatment of breast cancer in 2008 was a close call

based on the results of a single positive trial in the face of a second negative trial. CDER's current recommendation to withdraw this indication is based on the totality of the data from five controlled trials that enrolled more than 3500 patients with breast cancer.

The totality of the data show that Avastin has only a modest effect on PFS, and this small effect, in the absence of an effect on overall survival or patient quality of life, does not outweigh its substantial and life-threatening risk. The lesser magnitude of effect on PFS alters the benefit-risk assessment of Avastin, and does not support continued approval.

Let me restate several important points. No clinical trial on its own, or the combined results of five clinical trials, has shown an improvement in overall survival. No post-approval clinical trial has shown an improvement in PFS of the magnitude seen in E2100. No clinical trial has shown an improvement in health-related quality of life. And all clinical trials show an increase in

serious adverse events with the addition of Avastin to chemotherapy alone.

Withdrawal of the indication for Avastin in breast cancer is clearly supported by the data from the available five adequate and well-controlled trials and is the right public health decision.

At CDER, we value the views and perspectives of those who do not agree with our decision, and we have carefully considered these views as we have reviewed the available data. In the end, CDER's decision must be based on the available scientific data from adequate and well-controlled trials. These data inform our assessment of the benefit-risk of the drug for the population of patients with breast cancer. That is our obligation under the law, and we take that obligation and our public health mission very seriously.

We stand ready to work with Genentech and others to design trials to divine what, if any, subpopulation of patients with breast cancer might derive benefit from this drug that outweigh its

risk. If such data are generated, a new science-based indication could be approved. Until that time, it is not appropriate for the drug to continue to be approved for the treatment of breast cancer when the totality of the available data does not support such an approval.

I will now review the questions posed to the panel for this hearing and restate CDER's answers.

On the slide is question number 1. The answer to this question is yes. The AVADO and RIBBON-1 trials, which Genentech designated as the confirmatory trials, failed to verify the magnitude of PFS that was seen in the E2100 trial and did not show an improvement in overall survival or quality of life.

Absent an effect on overall survival or improved quality of life, which we consider measures of direct clinical benefit, the modest effects on PFS are not enough to confirm clinical benefit in light of the serious risk associated with the use of Avastin.

Here are the two questions labeled number 2.

The answer to these questions is also yes. The totality of the data demonstrate that Avastin has not been shown to be safe and effective for the treatment of breast cancer. Four of the five trials that Genentech submitted in support of this indication showed no effect or only a small effect on PFS, and none of the trials showed that Avastin improved overall survival or quality of life. All trials showed an increased risk of serious side effects. Therefore, the benefits of Avastin do not outweigh its risk for the treatment of breast cancer.

On the slide is question number 3. The answer to this question is no. The accelerated approval program is built on the foundation that approval may be withdrawn when post-approval trials fail to confirm clinical benefit, or when the evidence establishes that the drug is not safe and effective for its approved indication.

In the case of Avastin, both of these conditions have been met. Permitting continued approval of Avastin for the breast cancer

indication while Genentech designs and conducts additional trials would be counter to the totality of the data, which support our conclusion that the benefits of the drug do not outweigh its risk in this disease, would not be in the interest of public health, and could jeopardize the integrity of the accelerated approval program.

Thank you, and that now concludes CDER's formal presentation.

DR. MIDTHUN: Thank you very much to our presenters from Center for Drugs. We will now break for lunch, but let me just draw your attention to the fact that there is an error in the program. There is one hour allocated for lunch. And so I would expect people to return in one hour from now, which is at 1:15. Thank you.

(Whereupon, at 12:15 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

Questions by Genentech

DR. MIDTHUN: Good afternoon. I ask everyone to please take their seats, and we will now proceed with the next portion of the hearing.

In this portion, Genentech will have the opportunity to question the CDER presenters. That will last an hour, and then we will have a session where the advisory committee members and I will ask the CDER presenters questions, and then we will break for 15 minutes between that portion and initiating the clarifying questions portion.

So let's start and we'll have one hour for this next session. Thank you.

MR. SCHMIDT: Thank you, Dr. Midthun. As we've heard today, this hearing is immensely important to patients, doctors, innovators, researchers, and research companies like Genentech. So we appreciate the opportunity to be able to ask CDER questions and to be able to present our case tomorrow, our views tomorrow.

Just to introduce us, my name is Paul Schmidt. I'm joined, on my right, by Dr. Philippe Bishop, who heads Genentech's development program for Avastin; and, on my left, by Dr. Jeff Helterbrand, who is the global head of biostatistics for all Genentech medications. And we'll take turns asking questions today.

CDER's presentation points out that there are very respectful but vigorous areas of disagreement between CDER and Genentech on what the data shows. But we believe there are also areas of agreement between the two sides, and that's where I'd like to start by asking some questions, where we agree on what the data shows and what conclusions we draw from the data. And I'd like to start with safety.

When we talk about safety, am I correct that CDER agrees that the label fairly describes the safety for Avastin?

DR. KEEGAN: Yes.

MR. SCHMIDT: And that safety has not materially changed from the time of accelerated

approval.

DR. KEEGAN: Yes.

MR. SCHMIDT: So what we're talking about today when we're talking about safety is we're not talking about a change in the safety since the time of accelerated approval, we're talking about an initial showing of benefit in E2100 that justified that safety profile, and CDER no longer believes that that safety profile is appropriate in light of its current views on the efficacy of Avastin.

DR. KEEGAN: Yes.

MR. SCHMIDT: And that's why, had the E2100 data replicated itself, in CDER's view, in terms of the magnitude of benefit, we wouldn't be having this discussion today. The benefit would outweigh the safety.

DR. KEEGAN: Correct.

MR. SCHMIDT: Okay. Now, the basis for approval in E2100 was the showing of PFS benefit in that study, with no detriment to overall survival; is that correct?

DR. KEEGAN: Correct.

MR. SCHMIDT: There was no showing of overall survival nor was there a showing of quality of life.

DR. KEEGAN: Correct. There was no effect on survival or quality of life.

MR. SCHMIDT: And CDER, as we understand it, adheres to the view -- and I'll read from CDER's summary of arguments. CDER has not changed its views regarding the usefulness of PFS as a clinical endpoint for the approval of cancer drugs and has not determined that an overall survival benefit is always needed in addition to a PFS improvement.

That's from CDER's summary of arguments. CDER in the past has received questions from the ODAC on this point and may receive questions on the meaning of progression-free survival as an approvable endpoint.

Today, does CDER stand behind those statements that progression-free survival can be an approvable endpoint and that overall survival is not always required?

DR. PAZDUR: Yes, we do; but it would have

to be considered in the context of a risk-benefit assessment, and one would strongly consider the magnitude of the effect in making a decision on that.

MR. SCHMIDT: Why is it that progression-free survival is an approvable endpoint, in CDER's view?

DR. PAZDUR: There has been a lot of controversy regarding the use of PFS as an approvable endpoint. Arguments that were made even in the December 2007 ODAC meeting pointed to the fact that there may be usefulness in the delay of therapies, subsequent therapies, or perhaps in the amelioration of symptoms that simply could not be picked up.

These are relatively theoretical points of view. They have not been shown, and we were willing to take that leap of faith to go in that direction in order to get cancer drugs out to the public.

MR. SCHMIDT: And would be again.

DR. PAZDUR: Yes.

MR. SCHMIDT: Let me take a different area where I believe we agree, and I'm actually drawing on slide 91, which, Dr. Keegan, was one of your slides, which quoted the 2007 guidance.

Am I correct that in assessing and interpreting the benefits and risks of a given medicine and, in particular, in weighing PFS benefit, CDER will look at what's known about the benefits and safety of other medicines that treat the same condition.

DR. KEEGAN: They will look at the disease itself and the available alternative therapy in order to put the risks and benefits in context.

MR. SCHMIDT: And, in fact, CDER has done that with respect to Avastin. It has looked at some of the other treatments that are available for first-line metastatic breast cancer and judging the efficacy of Avastin; is that correct?

DR. KEEGAN: Since this was an add-on therapy to standard therapy, what we were looking at was the incremental benefits and the incremental risks.

MR. SCHMIDT: Well, CDER has also compared the Avastin data at different times to Gemzar and Herceptin data; is that correct?

MS. BRANDEL: I would just like to remind everyone that according to the ground rules set out in the notice of hearing, decisions regarding other products would not be considered relevant to this proceeding.

MR. SCHMIDT: Well, I'd like to request an answer to that question. I'm asking about the data.

Am I correct that in its approval documents relating to Avastin in metastatic breast cancer, CDER has looked to data on other treatments for the same disease?

DR. KEEGAN: Could you clarify which documents you're referring to?

MR. SCHMIDT: Sure. Why don't we put up document 39, please? And let's go to page 4 of this document. Before we go to page 4, let's look at the cover page. This is the office director's memo from December 15th, 2010 in connection with

the NOH decision.

Dr. Pazdur, your name appears on there. Dr. Jenkins, you appear on there, as well.

If we go ahead to the fourth page of this document and look under the conclusions, paragraph numbered 1, we see references about halfway through that paragraph to data for Herceptin and Gemzar.

That's not uncommon to do that, is it?

DR. PAZDUR: No.

MR. SCHMIDT: To reference other data for other medications that treat the same condition; correct?

DR. PAZDUR: Correct.

MR. SCHMIDT: Thank you. Let me touch on one other area where I think the parties have agreement. It's actually something that Dr. Midthun spoke to at the very beginning of the proceeding.

Are we in agreement that there is unmet medical need for HER2-negative metastatic breast cancer?

DR. PAZDUR: Which line of therapy are you

speaking of? Just in general in breast cancer?

MR. SCHMIDT: In general, yes.

DR. PAZDUR: In general, for breast cancer, yes, there would be a need for other therapies. For first-line breast cancer, there are many approved therapies.

MR. SCHMIDT: Okay. Well, let me ask about that. Am I correct that in the past 30 years, there has been only one other non-hormonal medication approved for first-line HER2-negative metastatic breast cancer? And I'm thinking specifically of gemcitabine, Gemzar.

DR. PAZDUR: I think that's right. I haven't looked at the data in some time. So I can't answer definitively.

MR. SCHMIDT: There are FDA documents I could show on that point, but in the interest of time, I'm going to jump to my next question, unless you'd like to stop and look at them.

The next question is, am I correct that the mature survival data for Gemzar did not show an overall survival benefit?

DR. PAZDUR: Yes. When we approved the drug, there was interim data that showed a p value less than .05. The numerical trend was maintained until the final, but it was not an overall survival improvement. The drug was approved on the basis of the PFS value.

MR. SCHMIDT: So am I correct that there has been no non-hormonal medication in the past 30 years that has shown, in the final study results, a statistically significant improvement in overall survival in the context of first-line metastatic breast cancer?

DR. KEEGAN: We've had several advisory committees providing advice on the appropriate endpoints for metastatic breast cancer, and there is a sense among the advisory committee and the community that, in fact, doxorubicin and even the taxanes provide a survival benefit. Those may not have been the basis for the approval, but they are, in fact, how we understand and think of those drugs today.

MR. SCHMIDT: My question was focused on

approvals in the last 30 years targeted specifically for first-line HER2-negative metastatic breast cancer.

Are there any in that setting that the final data has shown an overall survival benefit?

DR. KEEGAN: Other than Avastin, there is no drug that carries that specific indication of HER2-negative metastatic breast cancer. So it's in a class by itself.

MR. SCHMIDT: You wouldn't include Gemzar in that group?

DR. KEEGAN: The indication isn't limited.

MR. SCHMIDT: Okay. I'm going to pass the questions now to Dr. Bishop, who is going to ask some questions on the safety profile of Avastin, which we've talked about, in terms of where it stands and the fact that it has not changed since the time of accelerated approval. And then we'd like to ask some questions about efficacy and how efficacy is measured.

DR. BISHOP: I would like to transition now to a safety issue that has been the subject, I

think, of discussion previously, but may have confused some. And specifically, I want to talk about the rates of death observed in the metastatic breast cancer trials in combination chemotherapy only and Avastin treatment arms.

To facilitate the discussion, I would like to show document 42, please. So what is shown here are the fatality rates observed in our studies, and the data is from our sBLA submission from the clinical summary of safety and the clinical summary of efficacy, which FDA, I believe, has reviewed.

You can see a column of the pooled analysis, and the first number there represents the chemo only arm -- I mean, the Avastin-chemotherapy arm, and the second number represents the chemo only arm, and the last column is from the E2100 data.

Now, focusing on the first row, we see that there are fewer total deaths in the Avastin-chemotherapy arm than in the chemotherapy arm, regardless of whether or not one considers all three first-line metastatic breast cancer trials at the approved dose or whether or not someone

examines the E2100 results alone.

Do you agree with that?

DR. PAI-SCHERF: I do not have the pooled data in my deck, but I will be happy to show the death rates of individual studies and we can walk over them, because I can show you the death-associated adverse events and how we assigned the relationship to treatment.

Would you permit that I go over those slides?

DR. BISHOP: So here we are focusing on E2100 versus the aggregate data, which represents 1,427 patients for the Avastin-chemotherapy and the chemotherapy.

DR. PAI-SCHERF: No. Actually, I am talking about in --

DR. BISHOP: Yes. So I think we'll have an opportunity to go over individual trials perhaps tomorrow when we present our studies. But it is fair to say that the FDA does look at aggregate data, including pooled analysis, when you make an assessment of death, especially in the context of

safety; is that correct?

DR. PAI-SCHERF: Yes. But in the case of the confirmatory trials, we looked at individual data, as well as the aggregates.

DR. BISHOP: Fair enough.

DR. PAI-SCHERF: And I would like to say that assignment of that in these trials were done by looking at individual patients who died on protocol, and, as you know, we look at any death and any serious adverse events on trial very closely and carefully.

We look at individual patients' case report forms, narratives, and, as you know, sometimes we'd ask for patients records in order to make our assignment. And the cases that I mentioned that died due to potentially related Avastin, they were assigned by looking at the data closely.

DR. BISHOP: But looking at the first row, this is the overall death that's observed and these are the facts of our submission.

So, in fact, for the Avastin-chemo, there were fewer deaths, 52 percent versus 55.8 in the

aggregate data, which I believe the agency looks at.

Now, with regard to attribution, is it also fair to say that when we look at deaths due to breast cancer or deaths to other reasons, that there were fewer overall deaths in the categories for the patients treated with Avastin and chemotherapy versus chemotherapy alone?

DR. PAI-SCHERF: The tables that I have show actually the deaths attributed to adverse events were either equal or slightly lower. However, as I stated, we look at individual cases and do our assignment.

In the case of Avastin, we are very aware of the toxicities, and, as you know, the label carries a black box warning stating that hemorrhage, GI perforation, fistulas can all cause death. And I think our findings are not different from what is in the label.

DR. BISHOP: And those deaths would be included in the deaths due to other reasons. This would be treatment-related deaths and missing or

unknown or other causes of death.

DR. PAI-SCHERF: Some of them, yes.

DR. BISHOP: And in these cases, then, we would view these categories as being important and I would suspect that CDER would agree with that.

DR. PAI-SCHERF: All deaths on protocol are very important. But may I add that death assignment in protocol in cancer patients with many co-morbid diseases and sometimes, because of the disease, can be difficult.

There are cases -- and one case here that we have a patient who developed wound healing complications and fistula and died a few weeks later and was attributed as causes other than to Avastin.

So death attribution is difficult, and being a reviewer with this product for almost six years, I see many cases coming to my desk. And my overall feeling is that the 1 percent attribution is a conservative number of deaths attributed to Avastin.

MR. SCHMIDT: Okay. We'd like to ask some

questions now about efficacy and specifically about the E2100 study and CDER's views on the E2100 study.

Before I ask that question, though, let me ask a general question. We heard today many moving stories from patients of Avastin who used the phrase "super responder."

Does CDER agree that there is some set of patients, breast cancer patients, for whom Avastin provides meaningful clinical benefit?

DR. KEEGAN: No, we do not agree.

MR. SCHMIDT: Well, let's talk about E2100 and what E2100 shows. E2100 was, of course, the government-sponsored study that was the basis for CDER's decision to approve -- to grant accelerated approval for Avastin with paclitaxel.

Am I correct that CDER requested that E2100 be subject to independent review and various sensitivity analyses on many of the points, many of the questions that have been raised today about E2100?

DR. KEEGAN: Yes, because of concerns with

regards to the completeness of the assessment, we did, and because of the open label nature of the trial and the subjectivity of the endpoint, we did request both an independent review, as well as sensitivity analysis to assess for the robustness of the results in light of the missing data.

MR. SCHMIDT: So to talk about some of the concerns, including the missing data concern -- and maybe I'll start off there -- were specific analyses done to ensure that missing data was not undermining the reliability of the results, and is it, in fact, true that CDER concluded that the amount of missing data was in line with the amount of missing data seen in other approvable trials?

DR. KEEGAN: So there were multiple issues, partly, the open label nature, which introduces some level of bias; partly, the lack of concordance; partly, the missing data. Multiple areas raised concerns regarding our confidence in the estimate that was provided.

There is no way that a sensitivity analysis can ensure that those problems have been addressed.

It is simply a way to assess what the potential impacts are. But sensitivity analyses will never be able to ensure or compensate for missing data or data conduct issues.

So it was simply a way to assess what were the possible ranges or limits, outside limits of the treatment effects that were being demonstrated.

MR. SCHMIDT: And just to follow-up on my question, which was more targeted, were, in fact, sensitivity analyses conducted to determine that the amount of missing data was not undermining the reliability of the results, and did CDER conclude that the amount of missing data was in line with that seen in other studies?

DR. KEEGAN: We did not conclude that the amount of missing data or missing information and data issues were in line with other studies. We found this to be different.

We found the lack of concordance with other studies to be different, and we did not use the sensitivity analyses to assure ourselves of any specific treatment effect, but to assure us that a

treatment effect did, in fact, exist and might possibly include the range now in the label.

MR. SCHMIDT: Thank you. Why don't we call up document 22, please? Document 22 is a copy of the February 21st, 2008 office director's memo, which we received a month or so ago in connection with these proceedings.

If we jump ahead to the fourth page of this document and we look at the second full paragraph, and let's look at the last two sentences.

They say, "Prespecified sensitivity analyses corroborate the maintenance of a treatment effect in handling missing data. Recent applications have had missing data similar to that observed in the current Avastin application," and then it goes on to discuss those applications.

That's another example of what I was talking about, about sometimes looking at data from other contexts.

Was that a correct statement when that was made?

DR. PAZDUR: Yes. I think, though, what I'd

like to point out is we agreed about there is a treatment effect here. The robustness issue is not in debate, in our mind.

The problem that we had with this application when it came in were many issues that each in themselves perhaps were not unprecedented. However, when you took a look at all of the issues under consideration, we really felt that there was a need to repeat the study.

Those issues included a single study, a second study done in -- a negative study done in the second-line study, a lack of reliability in radiological reviews, almost a third of the patients not followed until a PFS event or end of study, and missing scans, about 10 percent.

Here, again, not one of these is unprecedented. However, once you start building a record here of multiple issues in an application, there is a problem which requires the study then to be replicated.

MR. SCHMIDT: Let me touch on some of those other issues. One of the issues, Dr. Keegan, I

believe you mentioned was the open label design.

Is it correct that most oncology trials have open label designs and that they've supported full approval for medicines like Gemzar, Herceptin, Tykerb and Ixempra?

DR. KEEGAN: I can't speak to the exact proportion that might be open label in nature. I can say that when we are aware of a study and we've discussed it in advance, or as soon as we've become aware of the study, as we were with E2100 that was ongoing, we advise that there be a prospective plan to assess the endpoint by an independent group masked to treatment assignment.

In some of the other studies you mentioned, that occurred prospectively, whereas it did not occur prospectively with E2100.

MR. SCHMIDT: Were those other examples I mentioned, in fact, examples of open label trials supporting approvals?

DR. KEEGAN: Open label trials where the prospective plan for independent evaluation of the subjective treatment endpoint was carried out, yes.

MR. SCHMIDT: Let me talk about the point about scan assessment, and then I'll move on to another subject.

At CDER's request, there was an evaluation conducted where the original investigators' assessments of the scan were tracked against assessments by independent review facilities.

Am I correct that CDER came to the conclusion -- and just so there are no surprises, I'm reading from the office director's memo again, that because of the close agreement between the two assessments, investigator and IRF, systemic bias seems unlikely?

DR. PAZDUR: Yes. Here, again, we agree that the effects on the primary endpoint were robust. Our major concern with this application, because it is being taken in a risk-benefit analysis, is what was the magnitude of the effect of the PFS, and that cannot be addressed simply by the sensitivity analyses.

MR. SCHMIDT: And, Dr. Pazdur, you may have just spoken to this in your answer. Shortly after

accelerated approval was granted, you gave an interview in the Cancer letter and stated that "E2100 trial was statistically robust. We are confident in an effect on the primary endpoint."

Was that a correct statement?

DR. PAZDUR: Yes, it is. And that was also stated in Dr. Lee Pai's initial presentations in the December 2007 ODAC.

MR. SCHMIDT: Let me turn to another topic. We've been talking about progression-free survival. I'd like to ask about another measure of benefit, which is one-year survival, the number of women alive after one year taking the medicine. And if we take the E2100 study, for example, the E2100 study showed a 7.4 percent absolute increase in the number of women alive after one year who used Avastin versus the number of women alive after one year who did not use Avastin. We heard one-year survival data cited today in the comments from one of the public speakers, as well.

My question is, does CDER consider that data, the number of additional women alive after

one year, to be relevant benefit data that weighs against the risks for a medicine like Avastin?

DR. PAZDUR: When we assess overall survival in making any overall survival claims, we would be looking at a log rank survival analysis, not a point estimate. I included the one-year survival in my office memo not so much as an efficacy issue, but one of safety, that patients were not succumbing to the toxicities of the therapy.

If one wants to start taking a look at point estimates or single points on a survival curve that are unspecified, it is tremendously treacherous to do so. If we take a look at your composite graph of the survival of all patients treated with Avastin from all of the trials, at three years, if I just pick that endpoint up, the placebo curve is actually doing better.

MR. SCHMIDT: And just to be sure I have your answer on that, as I understood your reference to one-year survival data in your office director's memo, you were balancing the one-year survival data against data on the risks of Avastin.

Is that a legitimate balancing to perform?

DR. PAZDUR: The toxicities were not causing deaths in patients at that specific time.

MR. SCHMIDT: So is that a relevant analysis to perform, one-year survival data weighed against some of the adverse event data?

DR. PAZDUR: I included it as a description of the effect of the drug and the toxicity of the drug.

MR. SCHMIDT: I'd like to ask a few questions about Study 10, given how prominently Study 10 featured in the presentation. In this phase 2 study, was the Avastin analysis the primary objective or an exploratory objective?

DR. KEEGAN: I refer to the Lancet article and not to a clinical protocol, so I can't answer specifically what the analysis plan was.

MR. SCHMIDT: Okay. Well, let me ask maybe a question that will short-circuit some other questions. Has CDER reviewed, to its comfort, the underlying data on Study 10 in detail, such as in a final clinical study report?

DR. KEEGAN: No.

MR. SCHMIDT: Is CDER aware that Amgen has submitted data to the agency suggesting that the study had a higher degree, for example, of censoring in the control arm with a larger PFS benefit as measured by the investigators?

DR. KEEGAN: No.

MR. SCHMIDT: That's not data that CDER has considered in citing Study 10.

DR. KEEGAN: I think your question was, was I aware of a submission, and I'm not aware of that submission.

MR. SCHMIDT: Okay. Has CDER reviewed any data underlying Study 10 to get itself comfortable that it's an appropriate study for CDER to be considering?

DR. KEEGAN: CDER chose that study because it was identified by Genentech as new evidence, and we looked first at the San Antonio breast cancer information that you cited and then later at the Lancet article when it was published.

MR. SCHMIDT: Okay. But has CDER conducted

the review of that study it would want to conduct in order to rely on that study?

DR. KEEGAN: For what purpose?

MR. SCHMIDT: For purposes of making approval or withdrawal decisions with respect to Avastin?

DR. KEEGAN: We were looking at it for purposes of supporting confidence in the magnitude of the effects cited in E2100 or not.

DR. JENKINS: And I would add to that comment. We made our recommendation in CDER for withdrawal of Avastin's breast cancer indication prior to our knowledge of the results of the Study 10.

As Dr. Keegan mentioned, Genentech made reference to Study 10 in your submissions. We've reviewed the manuscript, and we view it as supporting information to help us understand all the data available, but we're not basing our recommendation for withdrawal on Study 10. But Genentech did submit reference Study 10 to us, so we thought it was appropriate to review it and

provide some information in context.

MR. SCHMIDT: But that review has not included a review of the underlying data for that study.

DR. JENKINS: It includes review of the manuscript published in Lancet, not a full study report submitted by the sponsor.

MR. SCHMIDT: Okay.

DR. JENKINS: But, again, Genentech submitted that study in reference to your submissions. So that's why we brought it up and looked at it. You referenced it as support for your case, so we looked at it to see what information we could learn from the case in the study relative to the points at hand.

MR. SCHMIDT: Okay. We'd like to ask now about some of measures used to assess Avastin's efficacy and to ask some more detailed questions about AVADO and RIBBON-1, and Dr. Helterbrand will be doing that.

DR. HELTERBRAND: Good afternoon. So whether improvement in progression-free survival

represents clinical benefit depends on the magnitude of improvement, according to CDER, and my questions are going to focus on the choices CDER must make to determine what is sufficient to be clinical benefit.

To help us, could I please see document 34? And this will lead up to our first question.

On this slide, I have summarized the relative advantages of choosing the difference in medians as a measure of magnitude of benefit versus the hazard ratio. The key advantage of the difference in medians is that it can be easily translated into a prolongation estimate, such as a weeks or months improvement.

One key advantage of the hazard ratio is that it uses all of the data from all patients rather than just reflecting a single point on the survival curve.

Additionally, the hazard ratio estimate is typically adjusted for randomization factors, such as ECOG performance status, in order to reduce bias in the magnitude estimate. And, finally, the

hazard ratio is the typical basis for study designs, as it is directly aligned with the primary hypothesis testing procedure used in survival trials, the log rank test or the stratified log rank test.

So my first question for CDER would be would CDER agree that this represents a reasonable characterization of the relative merits of these two measures of magnitude?

DR. SRIDHARA: Yes, and that's the reason that we look at both of them. Hazard ratio doesn't give us the time that's there. For example, a change in two months to four months versus a change in 12 months to 24 months, under certain assumptions, you can say that the hazard ratio is .5 in both cases.

So in order to understand what's the temporal implication of this, we do look at both of them.

DR. HELTERBRAND: So in the Avastin case, CDER has chosen to emphasize the difference in medians as the measure of magnitude, as we saw with

the presentation this morning.

Now, would CDER agree that the outcomes of all patients are important, not just those of the median patients? And moreover, would CDER agree that the hazard ratio results from studies should not be ignored? And based on your response, I would say that you would not ignore the hazard ratio.

Can you confirm?

DR. SRIDHARA: Hazard ratio was certainly taken into consideration. Again, we don't look at it in isolation and we do look at the difference in medians.

So we have had applications where the hazard ratio was .5 and, in fact, the difference in PFS was just two weeks. And so where do we take that then? Yes, the hazard ratio was small enough, but the difference in medians was too small to be clinically meaningful.

So from a statistical point of view, the study was designed to test the hazard ratio. It did show a statistical significance. I don't think

we are questioning here that there is statistical significance. However, then it goes to the clinical team to assess whether this is clinically meaningful, and that's where the median differences also come into the picture, along with the hazard ratio.

DR. HELTERBRAND: So now we have the hazard ratio and we have the difference in medians, multiple measures of magnitude to consider. But that does cause some ambiguity.

If both measures are important, does that mean CDER is looking for studies to achieve a certain magnitude of improvement for both the hazard ratio and the difference in medians that is of two hurdles?

DR. SRIDHARA: It depends on the endpoint. If it's overall survival, it is difficult to pinpoint what median difference is good enough or what is not. However, in progression-free survival, when the assessment is based on the frequency of measurement, it's actually timed to radiographic scanning rather than actual

progression. And so we need to look at these types of median differences, as well.

DR. HELTERBRAND: So the answer is, yes, you have to -- there is a median threshold on the difference of medians that needs to be met, as well as a threshold for hazard ratios?

DR. SRIDHARA: The threshold is dependent on what is generally considered as a clinically meaningful and where is the stage of the disease and different diseases themselves.

So a lung cancer cannot be equated to a breast cancer or to a prostate cancer. So it really depends on the disease and the stage of the disease to come up with what this threshold should be, and we usually refer that to the clinicians. And I believe right at the beginning of the study, when the study is being designed, you are looking at what is clinically meaningful.

When you are powering a study for survival, the PFS will have more than enough power to show a very small difference. So statistically significant differences doesn't always mean that

they are clinically meaningful.

DR. HELTERBRAND: Okay. Let's turn to determining what magnitude of progression-free survival an Avastin trial must achieve to be considered clinical benefit, as this would greatly help us in designing a new trial.

Could I please see document 36? This will help. And this document probably requires a little -- this figure requires a little bit of explanation.

So to orient everyone, what I've plotted here are the observed hazard ratios for the E2100 study, the AVADO study, and the two cohorts in RIBBON-1. The scale goes from a hazard ratio of 0.4 to a hazard ratio equal to 1, where hazard ratio equals 1 means no benefit.

I've included the difference in the medians for each study in brackets. For reference, I've included the PFS hazard ratio and difference in medians for the Gemzar study with paclitaxel, since Gemzar is the only other recently approved non-hormonal medicine for first-line HER2-negative

metastatic breast cancer.

We see that the AVADO and RIBBON-1 studies were positive studies based on their prespecified primary analyses, with hazard ratios less than .7, far away from 1. Also, we see here that their hazard ratios for RIBBON-1 and AVADO bracket that seen with Gemzar.

So then my first question really is we see that the AVADO study had a hazard ratio of 0.62. Has CDER taken the position that this magnitude of PFS improvement is insufficient to represent clinical benefit for Avastin; and, if so, what improvement between that seen in E2100 and that seen in AVADO should Genentech design a new study to achieve?

DR. PAZDUR: The decision to approve a drug is not based solely on a hazard ratio. It is not based solely on the median difference. It is not based on a p value. But it is based on a risk-benefit analysis.

We cannot give you a specific number or a specific hazard ratio that would warrant an

approval or a non-approval. It has to be placed in the context of a risk-benefit analysis.

If you're looking for what is the PFS magnitude that we would be looking for, for Avastin in a first-line breast setting, I would refer you to the ODAC meeting of December 2007, the original ODAC meeting, where your own consultants were here and were exulting the benefits of a 5.5-month advantage in PFS, as well as the corresponding hazard ratio that went with it.

The bottom line is we don't approve a drug on a hazard ratio. We don't approve a drug on median differences. We approve the drug on a clinical determination of the risks and the benefits of the drug.

DR. HELTERBRAND: So CDER and Genentech have come a long way together on Avastin, with nearly 3,000 patients enrolled in first-line trials. But is it fair to say then that CDER is reluctant to communicate what measure of magnitude it's going to emphasize, such as the difference in medians or the hazard ratio, as well as what magnitude of

improvement it will need to achieve for CDER to conclude it provides clinical benefit?

DR. PAZDUR: We are not reluctant to specify a specific number. However, it is impossible to do without looking at it in the context of the toxicities and the safety profile of the drug. Here, again, we do not approve a drug on a hazard ratio. We approve the drug on the clinical judgment of a risk-benefit decision.

DR. HELTERBRAND: So in line with that, when did CDER inform Genentech that it was going to choose the measure to be emphasized, as well as the magnitude of improvement that needed to be achieved in the confirmatory studies?

DR. KEEGAN: As Genentech is aware, the confirmatory studies had completed enrollment and there was no possibility for us to affect the results of those trials. Therefore, there was really no point in commenting on it. You agreed to provide us the data and we agreed to look at it.

DR. HELTERBRAND: Since that time, though, in the summary documents we've seen, the point has

been that if we see the same magnitude of effect in a subsequent trial, as E2100, is that based on the median difference -- difference in medians or is that based on the hazard ratio? Is that your position?

DR. PAZDUR: Here, again, the decision to approve a drug is based on not a median, not a hazard ratio, but on a risk-benefit decision. I believe if we had data that confirmed either the median or the hazard ratio of the original E2100, we would not be here today.

The situation here is, again, it's a clinical decision that we're making as far as a risk-benefit decision, not simply looking at a hazard ratio.

DR. HELTERBRAND: So I have one last question then. So can I confirm then that for Avastin plus paclitaxel, CDER is requiring a more impressive progression-free survival hazard ratio, and median difference for that matter, than what was seen for Gemzar plus paclitaxel in order to conclude --

DR. PAZDUR: You cannot make that --

DR. HELTERBRAND: -- Avastin provides clinical benefit?

DR. PAZDUR: No. I would totally disagree with you on that point. As I stated before, for the fifth time, we are not approving a drug on a hazard ratio. We are approving it on a risk-benefit ratio and there are major differences in the toxicity and side effect profile of gemcitabine and Avastin. Gemcitabine does not have a black box with almost a -- what percent perforation was on it; 1.2 percent -- and other toxicity profiles.

Here, again, there is no such thing as an absolutely safe drug, but one has to take a look on an individual basis of the risk-benefit of that drug.

DR. HELTERBRAND: Thank you.

MR. SCHMIDT: Let me follow-up on some of the quality of life points that were made. Are there any patient-reported outcome endpoints for metastatic breast cancer that CDER has determined to be meaningful and valid to enable a labeling

claim in metastatic breast cancer?

DR. KEEGAN: I can't answer specifically for metastatic breast cancer. However, the agency has looked at use of pain endpoints for prostate cancer and has certainly considered symptomatic relief, carefully collected in a placebo-controlled trial, as being a potential way to demonstrate that the patients have achieved benefit or that the changes in tumor size or delay in time to progression might in some concrete way benefit patients.

MR. SCHMIDT: So I think we're on the same page, but to make sure we are. Have there been any approvals that CDER can point to in the metastatic breast cancer area based on quality of life data?

DR. PAZDUR: No.

MR. SCHMIDT: In 2006, Genentech met with CDER regarding the RIBBON-1 study, and I'd like to show you CDER's minutes from that meeting, document 8, please. If we look at the top, we see the FDA letterhead. We see the date February 8th, 2006, Type B meeting minutes from a teleconference on January 10th, 2006.

I'd like to look at the second page of this document, and if we could go to the second paragraph up from the bottom of the page, where it says "discussion" up there. Let's blow that up.

This is a discussion of the RIBBON-1 study. Is the panel familiar with this document?

DR. KEEGAN: Yes.

MR. SCHMIDT: The specific question I'd like to ask is there's a discussion in this paragraph and elsewhere in the document about using different chemotherapy arms in the study, which is how, in fact, the study was designed, as we saw during CDER's presentation.

CDER concludes by saying, "FDA understands that the treatment effect will vary according to the chemotherapy regimen used. However, the treatment effect must be efficacious for the combinations of bevacizumab and Avastin and chemotherapy used."

Am I correct in understanding from that quote that the FDA recognized -- and I'm reading from the quote -- that "the treatment effect will

vary according to the chemotherapy regimen used”?

DR. KEEGAN: The context of this discussion occurred following the results of the AVF2119g trial, where we were aware that there was no evidence of a benefit demonstrated in a large, randomized, well conducted study in combination with capecitabine for reasons that, at that time and to the present, remain unexplained. Therefore, FDA requested that there be sufficient numbers of patients studied to independently evaluate that cohort.

Other than that, FDA has only asked that there be exploratory analyses conducted to look at the consistency of the treatment effect, assuming that it will not be identical, but certainly not dissimilar, not contradictory, between one chemotherapy partner and another, and this is just a prudent means of exploration, as we do many subset analyses.

MR. SCHMIDT: Exploration recognizing that there could be differences in the treatment effect based on the chemotherapy partner, and, in fact,

that's what had been seen in 2119 versus E2100.

DR. KEEGAN: To clarify, we don't know why that treatment effect was different. Our interpretation is that, in fact, the treatment effect may have been -- has been overestimated by E2100 and is probably down to the lower end.

The actual treatment difference at medians was 0.7 months, relatively close to what we saw with the AVADO trials. So it may be simply that there are smaller effect sizes and the trial couldn't identify it, but we don't know that it is the chemotherapy partner, per se, or that Avastin is not effective or effective in a particularly strong way when given to patients in combination with chemotherapy for metastatic breast cancer.

MR. SCHMIDT: At the time of this document, though, CDER wanted to test the possibility that the treatment effect may vary according to chemotherapy regimen; correct?

DR. KEEGAN: We wanted that possibility tested.

MR. SCHMIDT: Okay. And that's what the

RIBBON design was set up to do, the RIBBON-1 design.

DR. KEEGAN: For the capecitabine cohort only.

MR. SCHMIDT: And is that why, also, when CDER approved Avastin based on E2100, it limited its approval only to paclitaxel, because that's the only place where the efficacy data existed?

DR. KEEGAN: That was the only place where both the efficacy and safety data existed.

MR. SCHMIDT: Okay.

Let me ask you about another point, Dr. Keegan, that you mentioned in your presentation. I put this out to the panel, but it came up in your presentation. Let's call up document 22, which is, again, the office director's review memo from February 21st, 2008.

If we look at the second page of this document, we see there's a heading about a third of the way down the page that says "AVADO trial," right above there, right above that paragraph. And then in the paragraph right below -- actually, the

last paragraph on the page, this section discusses the AVADO study.

This paragraph, in particular, cites the median PFS difference that was demonstrated in the AVADO study, and it shows that there was a .8-month median PFS difference as the final PFS difference, as we know, from the final data in the AVADO study.

It goes on to reference -- before talking about median PFS, it talks about the hazard ratios, highly statistically significant. It goes on to discuss the objective response rate, and then it goes on to say data is immature regarding 2(a) survival analysis, with less than 20 percent of patients having an event on either arm, no characterization of what the survival data shows.

My question is this. When CDER received this document showing a final median PFS difference of .8 months, at any point in time, did CDER say to Genentech that that difference in median PFS would be insufficient to support approval for Avastin?

DR. KEEGAN: I would have to go back and check records on our totality of communications. I

can’t answer that.

MR. SCHMIDT: I only get to question you today. So is there anything you can point me to today where CDER said to Genentech -- AVADO became a confirmatory trial for E2100; correct?

DR. KEEGAN: Correct.

MR. SCHMIDT: So in accepting AVADO as a confirmatory trial, was there any point in time -- Genentech had the understanding that CDER was accepting the hazard ratios as proving the magnitude of benefit.

Did CDER say at any point in time that you can point me to here, that a .8-month median PFS difference would not be enough?

DR. PAZDUR: Let me put this in context. When we were making the decision on the E2100 trial, we were aware that there was going to be an announcement of two trials, the RIBBON-1 trial and the AVADO trial. Before we wanted to make a decision on that, we asked for top-line results of the AVADO trial, because it was the one that was most mature. I believe a series of 20-odd slides

came to us with top-line data. We considered this data very premature.

Our purpose in requesting this data was not to review it. We did not know the status of the review as far as would this information hold up under FDA review. It simply was to ask if the trial was going to be reported out as a negative or positive study.

Since the controversy of the E2100 decision was going to be announced, we did not want to go out on a limb when shortly thereafter, potentially, a negative trial was going to be announced.

I believe these were also the slides that you showed a potential hazard -- I mean, an analysis of overall -- of survival, I should say, with a p value that was circled that was pointed in a statistically significant lean, so to speak.

Here, again, I think it's an issue that we have discussed at the original December 2007 ODAC meeting, the need for a magnitude to be demonstrated here.

The bottom line is we are looking -- and

Genentech knew this -- for a clinical benefit to be demonstrated in one of these trials or in any trial that they chose to give us for an accelerated approval confirmation. All we wanted was one single trial to show a clinical benefit here, and they could select anything they want or come up with new studies.

MR. SCHMIDT: Well, I appreciate that context. Let me come back to my question. The company thought that AVADO was clinical benefit. My question is, at any point in time, having this data in hand, having accepted AVADO as a confirmatory trial, did CDER say to Genentech that .8-month median PFS difference will not be enough to support approval?

DR. PAZDUR: I do not believe we did that.

MR. SCHMIDT: Thank you.

I hope you have a sense from the comments and from some of our questions how the company has struggled to understand what the approval standard is.

Is there any clarity you can give us on that

today in terms of the median PFS showing that would be required to support full approval?

DR. PAZDUR: As I said, the approval process is not about a median PFS; it's about a risk-benefit decision. At the end of the day, you have to show a clinically meaningful impact in a risk-benefit analysis.

So a magnitude of the PFS change has to be viewed in the context of the safety profile of the drug, the context of the disease setting, existing therapies of the drug, the performance status of patients, et cetera, the other clinical aspects that would come into play here. So for me to give you a number of a hazard ratio would be impossible to do.

MR. SCHMIDT: Let me ask some questions about the standards that apply in this context. There was a legal presentation at the beginning, and I'd like to follow-up on that by asking about CDER's understanding of the standards and the authority that the FDA has under the accelerated approval decisions.

Do you agree that FDA has the discretion to decide that withdrawal may not be appropriate, even if the confirmatory trials for some reason fail to confirm clinical benefit, if there is still a sufficient showing of clinical benefit from the data that supported approval in the first place?

Does CDER have that discretion?

MS. BRANDEL: The statute and the regulations authorize CDER to withdraw approval under specified circumstances. They say that we may withdraw. However, it's the view of the CDER scientists that two of those criteria are met here, which means that our standard -- we've met the legal standard for withdrawal.

MR. SCHMIDT: And, Ms. Brandel, I'm trying to understand CDER's conception of that standard. You just referred to CDER "may" withdraw. Would you agree that CDER has discretion, where CDER thinks it's appropriate, to determine that withdrawal may not be appropriate, even if a confirmatory trial for some reason doesn't truly confirm, or is withdrawal mandatory in all

circumstances?

MS. BRANDEL: No. It's the former.

MR. SCHMIDT: There is discretion.

MS. BRANDEL: Yes.

MR. SCHMIDT: Okay. Could you give us guidance as to when exercise of that discretion would be appropriate?

MS. BRANDEL: We have said before that our regulatory approach has to be governed by the unique factors of each particular case and that some of the factors that CDER will consider are the benefits of the drug, the risks of the drug, whether a drug is the only therapeutic option available for a disease, and perhaps even the reasons why post-approval studies did not confirm clinical benefit.

MR. SCHMIDT: Will CDER also consider maybe this falls under the point about the only therapy? Will CDER also consider the generally unmet medical need and the disease state?

DR. JENKINS: I think we consider a lot of factors, as Ms. Brandel just mentioned, including

the factors that she mentioned. Whether this is a continuing unmet medical need is something we would consider.

I think we also consider how much data are available. In this case, I don't know if we've had a case like this before where we've had 3,500 patients studied in the total database for the indication. So we also have to look at the magnitude of the data available to inform the benefit-risk decision for the particular drug.

MR. SCHMIDT: The European Medicines Agency has retained full approval for Avastin with paclitaxel. The National Comprehensive Cancer Network continues to endorse Avastin with paclitaxel. We are not suggesting nor have we ever suggested that CDER is bound by those determinations, but my question regarding those determinations is this.

Does CDER agree that the EMA determination, which I think we would agree reflects a different view of the data than CDER has reached, and the NCCN determination reflect reasonable alternative

views of this dataset?

DR. JENKINS: We made our decision independent of other decisions that may have been made by EMA or the NCCN. We looked at all the data available and made our decision based on the benefits and the risks of the drug. We had conversations with EMA about their thinking about the data. I'm not aware that we've had any conversations with the NCCN about their recommendations. As I understand it, that's a practice guideline, that's not a regulatory body that's making a decision based on the standards of law and the data.

We acknowledge that we reached a different conclusion about the data than EMA. That's not unusual. We do occasionally reach different conclusions about drugs than the EMA does, and, in fact, with Avastin, in particular, we approved Avastin for glioblastoma, and the EMA looked at the same data and concluded that they would not approve it for that indication. So it's not that rare that we don't come to the same conclusion looking at the

same data.

MR. SCHMIDT: And let me come back to my question. My time is short, so I'd ask for a yes or no, or if you can't answer yes or no, please let me know.

But my question is, simply, recognizing the EAM came out at a different place, recognizing that NCCN came out at a different place, does CDER recognize those as legitimate alternative views of the data?

DR. JENKINS: Those are different judgments that have been made by different groups of individuals. As I said, we made our decision independent of others based on the data we had in front of us and all the factors that we've talked about today.

MR. SCHMIDT: Can you answer whether you think those are legitimate alternate views of the data, reasonable alternate views of the data?

DR. JENKINS: Well, I think the EMA is a recognized regulatory body. We have a lot of interactions with EMA. We don't question that they

reached a different decision than we did. As I said, we don't always reach the same decisions as EMA and, as I pointed out, we reached different decisions on breast cancer for Avastin and for glioblastoma for Avastin.

MR. SCHMIDT: Okay. Let me close by asking a final line of questions. I hope you would agree that in the time since the 2010 ODAC and since CDER's action following the 2010 ODAC, Genentech has looked for ways to address the concerns that CDER has raised in a way that would keep Avastin available for patients, and that includes going into the ODAC seeking full approval across a variety of chemotherapy partners to only seeking to retain accelerated approval with paclitaxel.

That includes proposing a specific confirmatory study designed to truly replicate E2100 in terms of being a paclitaxel study, with a biomarker component. And that includes being open to and discussing the possibility of label changes that would address or attempt to address the points that CDER has raised regarding Avastin, both the

efficacy data and the safety data.

Given the high unmet medical need for this disease and the many supporters of Avastin, are there other steps that CDER has considered and raised with Genentech designed to try to keep this medicine available for patients with metastatic breast cancer?

DR. JENKINS: I think we reviewed the data and decided that the benefits don't outweigh the risks, which is the standard for approval.

I'd have to turn to my colleagues to see if there have been other discussions. But I think we concluded, as we issued in the December 16th decision, that the benefits don't outweigh the risks, and that's the statutory and legal standard for approval. So I'll stop there.

MR. SCHMIDT: If I may ask one short follow-up question. Is there any proposal that anyone on the panel can point us to that CDER has considered for keeping this medicine available for metastatic breast cancer patients?

DR. KEEGAN: No.

MR. SCHMIDT: Thank you.

Questions by Advisory Committee and Presiding Officer

DR. MIDTHUN: Thank you. That concludes that portion. And now we'll move to the portion where the advisory committee and I can ask questions of the CDER presenters. And if you would just indicate who would like to speak. Dr. Wilson?

DR. WILSON: Yes. Thank you. I have several clarifications and one question.

One clarification I would like is regarding the lack of approval of only one -- or the absence of approval except for one drug in HER2/neu negative upfront breast cancer of the last 30 years.

I was a little bit confused by that, because the recognition of HER2/neu negative breast cancer as a clinical entity has really only been known for approximately one decade. So how could FDA be approving drugs for a biologic entity that did not exist more than about 10 years ago?

DR. KEEGAN: That's why I said that this

drug was somewhat in a class by itself, because, in fact, this was, I think, the first studies that we had received where the eligibility criteria specifically excluded patients who were HER2 positive.

DR. WILSON: So just to be clear, then, the question that only one drug has been approved in the last 30 years isn't really relevant, because for most of that time, this has not been a recognized group.

My second question regards the toxicity that we saw in the presentation of their being equal or maybe, in some cases, slightly higher percentages of death in the non-Avastin group. And I was a little bit concerned about the lack of recognition in that data, at least in terms of the questions, that may be driven specifically by the actual drug itself.

So inherent in the questions that I heard to you, it sounded as though that as long as the overall death rates are equivalent between two arms, that one would ignore the fact that a drug

could specifically cause deaths such as those associated with lethal hemorrhage or something like that.

DR. KEEGAN: Well, I think, as Dr. Pai-Scherf said, she definitely considered the deaths that were attributable, as well as -- I'd like to say that the focus on deaths is highly limiting. I think we considered the totality of the data as we received it, which, in E2100 and in RIBBON-1, were actually somewhat limited to only serious or life-threatening events. So we looked at everything, not just deaths.

DR. WILSON: Right. So, therefore, it is very critical to recognize that there can be drug-specific deaths and to look at the totality of deaths on both sides doesn't give you the real assessment of the risk-benefit.

My final question regards the relative timeline for when the E21 trial was brought forward for approval. One generally does not think of the cooperative groups as the venue through which a drug company is going to be specifically designing

and running clinical trials for regulatory approval, but the cooperatives may be doing them for academic or clinical reasons.

So I'm trying to get a sense of when the AVADO and the RIBBON trials were running relative to the E21. Were these trials running and were they the drug company trials that were really the ones that Genentech was using to try to get regulatory approval and there was a fortuitous positive result from the E21 trial and that's why that was brought forward?

DR. KEEGAN: So, actually, the chronology pre-dates both E2100 and AVADO and RIBBON-1. The original trial that Genentech identified as the basis for seeking an approval in metastatic breast cancer was AVF2119g. While that was ongoing and prior to the study results being released, we were made aware of Genentech's interest in the E2100 trial, which was also ongoing. So after the negative results of AVF2119g, E2100 is identified as their lead trial.

We were also made aware of the RIBBON trials

during their development. But the AVADO trial was not brought to our attention until approximately the time of the ODAC, nearing the end of the review of the original efficacy supplement, and that was not a trial that we were involved with or considered in any way as part of the development program, at least under the U.S. approval.

DR. WILSON: Then my final comment would be, is it fair to say that, in general, the intent of cooperative group trials really don't focus on regulatory approval, but they are designed and their quality assurance, et cetera, is really at a different standard? So is it fair to say that they are not really your mainstay for regulatory approval, in general?

DR. PAZDUR: I think the E2100 is a very good example of what happened at that time. Obviously, a CR letter went out because there were significant problems with that trial in terms of missing data, et cetera, and Lee could go over it in detail, if you wish.

We've worked with the cooperative groups in

earnest to emphasize that, please, identify studies prospectively, if you're going to bring them in, so we can ensure the adequate safeguards; i.e., end of phase 2 meetings, special protocol assessments, discussion of what data is needed, prospective evaluations of radiographic endpoints being stipulated in the protocols.

This occurred early, obviously. This trial was initiated in --

DR. KEEGAN: 2001, I think.

DR. PAZDUR: 2001. So it really was outside of where we really started looking at cooperative trials. But the problems that we had with E2100 were really very reflective of a study that was done not for regulatory purposes, but really for some type of publication, et cetera.

Lee, I don't know if you want to comment on the problems that you saw with E2100 right from the beginning.

DR. PAI-SCHERF: The data collection was very poor. At the time the study was designed, Avastin was not even approved, and they did not

collect the grade 1 and 2 toxicities and adverse events leading to drug discontinuation in laboratory. Even ECOG performance status was not collected in this study. So we had a lot of insecurities concerning the data.

DR. WILSON: So the regulatory rigor of that trial was not really up to top drawer; correct?

DR. PAI-SCHERF: That's correct.

DR. WILSON: Thank you.

DR. MIDTHUN: Dr. Balis?

DR. BALIS: I'm going to ask this question tomorrow and see if we get the same answer. But we talked a lot about the data, and sometimes subtle differences or differences in outcomes of studies can be related to subtle differences in patient populations who go on those trials.

In your review of this study, either the eligibility criteria or the patient characteristics, is there anything that you noticed in looking at that data that could account for differences in outcome?

One of the reasons I ask is because if you

look at the outcome in the control groups, granted, sometimes the chemotherapy was somewhat different, there were some pretty significant differences in the control population outcome as well as the study population. And these trials were done in multiple countries and sometimes in different countries going across.

DR. PAI-SCHERF: Can I have slide 56 of the backup deck? These slides give a summary of the key demographic characteristics.

DR. PAZDUR: Closer to the microphone.

DR. PAI-SCHERF: Oh, sorry. Key demographic characteristics and prior therapy. Across the three studies, the median age was around 55. The majority were white. Forty percent or more had more than three metastatic sites. And the E2100 had 30 percent triple negative, while the other studies, around 22, 23, 24.

In terms of previous therapy, between 38 to 50 percent had received prior hormonal therapy, and these were for hormone receptor positive patients, and then 36 to 45 received hormonal therapy as

metastatic.

In terms of adjuvant chemotherapy, as you can see, 45 percent in the taxane-anthracycline had received adjuvant chemotherapy, while in the capecitabine arm, 72 percent had received adjuvant chemo.

If you break it down to the type of adjuvant chemotherapy, in the E2100, 20 percent had received prior taxane, while in the capecitabine cohort, double of that, 40 percent had received prior taxane. And the prior anthracycline is shown there, 50, 30, 63, and 31 percent in the anthracycline.

In terms of -- well, someone brought it up about this group of patients have no other choices. And as you can see, a large number of patients had not received prior taxane. Another half had not received prior anthracycline, which are considered the most effective agents we have for these patients.

DR. MIDTHUN: Please, Dr. Freedman.

DR. FREEDMAN: Thank you. I have a question

about the taxane refractory population in the E2100 study. Assuming that those patients who had a treatment-free interval of, say, less than 12 months, which they were included in the study, was there any difference between the arms in terms of the frequency of the patients who were likely to be more taxane-resistant as a result of the use in the adjuvant setting in a shorter timeframe?

I don't know if you've got that information. Maybe it's a question we should bring up tomorrow, but if you have it --

DR. PAI-SCHERF: I don't have data in hand right now. We will get it to you.

DR. FREEDMAN: I have another. And the other question relates to the indications that are approved in the label, attached to the label. We all agree that that's very critical both for the physicians and for the patients who they treat.

Given the results now that we have of several trials, does society have the same level of confidence in the information that's currently approved in terms of accuracy with regard to -- not

with regard to toxicity, because we accept the fact that that hasn't changed, but with regard to efficacy?

In other words, the docs, potentially the concerns about the earlier trial, E21, and how it was done and the subsequent trials not showing the same degree of efficacy, is this information that physicians and patients should have? Of course, it's not in the current label.

So I think that's the one question. Then I have a related one to that.

DR. KEEGAN: With regards to the dose of Avastin, it, I believe, did differ across the trials, but the average dose, weekly dose, is usually what was targeted, something on the order of 5 milligrams per kilogram per week. So it's either 10 every two weeks or 15 every three weeks, that sort of thing.

DR. FREEDMAN: So, actually, what I'm getting at is now you've got the results of the confirmatory trials that were supposed to be confirmatory, but they were not, so you do you

think that the label indication is still accurate in terms of its presentation of efficacy and toxicity?

DR. KEEGAN: No. We don't think it's accurate. It's listed as being safe and effective, and that is no longer our position.

DR. FREEDMAN: That's what I wanted to be sure of. Another question is -- and this was raised in the public session. People asked those patients who were already on treatment and who are getting benefit or they feel they're getting benefit and their physicians feel they're getting benefit.

Is there any mechanism by which the approval could remain for those patients who are already on treatment and experiencing benefit, even if the intent is to remove the label indication?

DR. JENKINS: I'll try to address that. As you heard, our view is that the benefits no longer outweigh the risks for this drug and, therefore, the standards for having this indication in the label no longer exist, and that's what led CDER to

recommend withdrawal.

The decision now rests with the Commissioner. If the Commissioner should uphold CDER's decision, I guess that would be the point to talk about any transition provisions for those patients who are already on the drug once the indication is withdrawn.

DR. MIDTHUN: Any other questions? Yes, please, Dr. Curt.

DR. CURT: Just a question of clarification to the agency. If an improvement in symptoms and a lack of alternative therapeutic options are two reasons for considering PFS as an approvable endpoint, does that mean that PFS is less robust in patients who are getting frontline therapy than in patients with refractory disease?

DR. PAZDUR: Yes. We, obviously, look at the disease setting. And when you have a first-line setting, we would expect a much more robust finding.

Obviously, in looking at a situation where we're dealing with a very refractory disease

population, with few therapeutic options available to them, there probably would be a greater degree of leniency in looking even at smaller PFS values to consider truly an unmet medical need.

This issue of an unmet medical need I feel really needs to be addressed, also. When we use that term in a regulatory context, what we're generally referring to is no available therapy. And I don't think anybody here at this time would say first-line metastatic breast cancer has no available therapy. And by available therapy, I'm talking about not only approved drugs, but drugs that are used commonly by physicians, such as CAF, you name it, Taxotere, Taxol, you name it, those drugs are available for a first-line therapy. In fact, paclitaxel is available therapy.

DR. CURT: Thank you.

DR. MIDTHUN: Yes, Dr. Sekeres.

DR. SEKERES: Just following up on that a little bit. There's no line in the sand that the FDA can draw about what's an acceptable PFS or hazard ratio, because it's a risk-benefit analysis.

Following up on what Dr. Curt just said, an unmet medical need and unavailability of other options for an at-risk population, like metastatic breast cancer, would also figure into that calculus; correct?

DR. PAZDUR: Yes.

DR. SEKERES: Yes. And that calculus then may change over time.

DR. PAZDUR: Correct.

DR. SEKERES: So a bar, if we imagine a bar, there is no absolute bar, that may have been acceptable 15 years ago or seven years ago may change as other therapies become available and are studied, whether on label or off label.

DR. PAZDUR: Correct. We have attempted to give consistent advice to sponsors and our advice is the following. Everyone would prefer to see a survival advantage in patients with breast cancer. So we would ask the sponsor usually to power a trial for overall survival, even if they plan on looking at progression-free survival.

We believe if you really never look and

don’t have adequate numbers to look at overall survival, we will really lose out in the long run and never identify drugs that have an overall survival effect.

So our current approach is please power these trials for overall survival. We are aware of the nuances that are associated with the interpretation of progression-free survival and they include, as we’ve had multiple discussions with the committee on, the accuracy of measurement, missing scans, et cetera, and, also, the subjectivity of the interpretation of clinical benefit.

So to really have a trial that has the ability to look at both endpoints is really what we’re really advocating sponsors do at this time.

DR. SEKERES: I’m sorry. One final question. We’ve discussed before on this committee when PFS can be acceptable, at least in our interpretation, and have brought up patient-reported outcomes. So in the absence of an overall survival advantage, if there is a PFS advantage and

a patient-reported outcome advantage, then potentially you could demonstrate benefit to patients.

The E2100 study had accompanying patient-reported outcome measures in the form of the FACT-B, but it was an unblinded study, so it's not as valid. The AVADO study also had a patient-reported outcome accompanying it in the form of the FACT-B, and that was a placebo-controlled study.

If that FACT-B with AVADO had shown some sort of magnitude of difference in patient-reported outcome, would that have been factored into the calculus for approval?

DR. PAZDUR: Yes. What we were looking for is one positive study here. The bottom line for this drug is we wanted one positive trial. That trial could have showed an improvement in overall survival. It could show a clinically meaningful progression-free survival; we brought the AVADO and RIBBON-1 trial to the committee and there was a unanimous vote that that did not exist, or it could have been some quality of life measurement.

All we're asking for here is one trial that shows clinical benefit.

DR. SEKERES: Thank you.

DR. MIDTHUN: Dr. Logan, and then Dr. Wilson.

DR. LOGAN: Two questions. The first one is about Study 10. I wanted to know, how does the study population compare to the E2100 study? Have you looked at that, since you have indicated that there may be some differences in the progression-free survival of the two control groups?

Also, how mature is the progression-free survival data in terms of how many events in that particular study?

DR. KEEGAN: As I said, what we were relying on is the Lancet articles and progression-free survival was, in fact, not the primary endpoint.

Since it appears the study might not have met its primary endpoint, I'm not really sure what you can say about progression-free survival, but we don't have all the details we would want on the number of events. We have the estimates that are

quoted in the article and the confidence intervals.

DR. PAZDUR: We acknowledge the limitations of this study. The reason why we brought it forward, it was included in the Genentech studies or Genentech's January submission.

DR. LOGAN: But it was a similar patient population.

DR. PAZDUR: Yes.

DR. LOGAN: Upfront --

DR. KEEGAN: Right. The eligibility criteria looked similar, from what we could tell; from the article. It's hard to tell, but there is some demographic data that suggest there might be some higher proportion of patients who were ER/PR positive, for instance.

DR. LOGAN: The second question I had was in terms of sensitivity analysis for the E2100 study in terms of the progression-free survival finding and the impact of the missing scans and the missing data in that study.

Did the sensitivity analysis give you any -- it's been mentioned that it gave you an

indication that the finding was robust. Did it give you any indication of potential variability and the magnitude of that effect on progression-free survival, and would that magnitude be consistent with these other studies that we're seeing?

DR. ROTHMANN: The sensitivity analyses that were performed by the sponsor, they performed six of them, had hazard ratios vary from 0.48 to 0.78, and FDA did some additional analysis, sensitivity analyses, I guess three of them, a couple of them being sort of worst comparison types, and those hazard ratios varied from 0.46 to 0.99.

DR. LOGAN: So there is substantial variability in the magnitude of the hazard ratio that is consistent, in fact, with these studies.

DR. ROTHMANN: Yes. Certainly, there is a wide variability in what these sensitivity analyses do.

DR. MIDTHUN: Dr. Wilson, and then Dr. Portis, and Dr. Curt.

DR. WILSON: Thank you. I wanted to get

your thoughts about how we think about the delta in the progression-free survival, which is, obviously, going to be a large driver of the hazard ratio.

From a patient's point of view, in the treatment arm, not the control arm, we want the drug to improve the treatment arm and we want that therapy to be significantly better than what we have out there.

What is interesting is as you go through these various trials, much of what seems to drive the difference is the control arm, not the treatment arm. In fact, the two trials that show the least delta in PFS, the E2100 and the RIBBON-1 capecitabine trial, both have the poorest control arm, whereas if you look at the variation in the treatment arms, there's not really a lot of -- I mean, there is some variation, but there's not a lot.

So I'm really struck by the fact that we're arguing here over E21 as being something that showed a robust finding, but if you look at it compared with the other trials, it's not at all

clear that this has added anything clinically meaningful.

Then if you actually go to the actual clinical trials and you look at the hazard ratios, what you find is among the taxane-based trials and you look at the impact of the Avastin, when the patient has had prior Taxol, that's where you see the impact of the Avastin showing up more, whereas if they haven't had prior Taxol, you see much less of an effect.

What that would tell me is that there is an awful lot of the -- that the benefit here is being highly driven by whether or not they are sensitive to the Taxol or not, and the Taxol is an approved, relatively safe agent.

So I just wanted to get your thoughts on this, because we're talking about these differences. However, it seems to me that, in many ways, it's the control arm that's shifting around here and not the treatment arm, and if there's not a lot of difference in the treatment arm and we have adequate therapy, which we clearly do with

some of these control arms -- docetaxel was 7.9, the Study 10, I believe, paclitaxel alone, was 10 months.

So if somebody wants to comment on that.

DR. PAZDUR: We noticed this, too. We had significant discussions about it. I don't know if Raj or the statisticians want to comment on it all, but this is something that caused us a lot of discussion internally about what was going on with these control arms, the exact reason that you're pointing out.

DR. SRIDHARA: I think it becomes very difficult to do cross-study comparisons of the control arms. So when this is an observation that we have seen of a control arm, it's not the same in all the trials, then we have to go back and look at were they the same population and were there some differences either in the ER/PR positive or HER2 positive. These were all supposedly HER2 negative. But in one of the studies, I think some HER2 positive patients were also included.

So it depends really on the baseline factors

and when we -- some we know that we have collected and we don't know about those we have not collected. So to do cross-study comparisons becomes very difficult.

DR. WILSON: Right. So I just want to finish up and say that I certainly believe that Avastin has clinical activity. It's a question of whether or not it's meaningful, and I think that one is not necessarily doing cross-trial trump comparisons when you look at the relative hazard ratios within the trials with regard to whether or not they're taxane-naïve or not.

The fact that the hazard ratios are changing on that tells me that a lot of that -- that there is biologic evidence that it's the Taxol that could be driving some of this and that there may not be the kind of benefit that one would hope when you add Avastin.

DR. MIDTHUN: Dr. Portis?

DR. PORTIS: Yes. I just want to clarify the findings that are presented about deaths, both in terms of -- adverse events first.

Is it so that there are more deaths due to adverse events in all the studies or in each of the studies presented? And then my second question is just about overall survival. Is it, in fact, true that there is no improvement in overall survival in any of the studies presented?

DR. PAI-SCHERF: Can I have number 77?

This slide shows the deaths on study in the AVADO with the ITT population. At the time of the data cutoff, it was a slightly numerically higher number of deaths in the Avastin, 7.5 in the 15 milligram arm compared to the placebo. The majority of deaths were due to disease progression.

If you look at the number of the adverse events, the deaths caused by adverse events, they were numerically equal. However, when we look at individual cases, as I mentioned earlier, there were two deaths probably associated -- most likely to be associated with Avastin. As I showed you, there was no survival advantage.

Next slide, please. And this is for the anthracycline cohort. The difference in number of

deaths in the Avastin arm and the taxane cohort was significant. It was 50 compared to 43. Again, if you look at the number of adverse event-caused deaths, they were also equal.

Next, please. And here I show you looking carefully at individual deaths, the taxane-Avastin arm compared to the taxane and placebo. They were equal in percentage, but if you look at the specific cases, there were three GI perforations and fistula abscess, there were two sepsis, which could be due to Avastin, but because the patient is on taxane, it could be both, while in the taxane in the placebo arm, there was sepsis, cardiopulmonary arrest, and PE.

If you look at the anthracycline and Avastin cohort, there was one GI perforation, one pulmonary hemorrhage, respiratory failure, and one suicide, while in the placebo arm, two neutropenia sepsis, one pneumothorax, and one PE.

When I state in my review that the deaths caused by Avastin are between .8 and 1.2 percent in this study, I take into consideration the careful

review of these cases in the population that received Avastin.

DR. PAZDUR: Could you put up Dr. Keegan's slide 125 from her presentation, because that has the pooled analysis of survival?

You wanted to know if there was any demonstrated survival, and I think this explains it. A picture is worth many, many words here.

The other issue that I wanted to bring this slide up, there was a discussion about this one-year survival rate. Please note, if one took a look at another non-prespecified endpoint, 36 months, three years, the placebo is actually doing better.

This is the problem with point analyses on a survival curve that are un-prespecified.

DR. PORTIS: Thank you.

DR. MIDTHUN: Dr. Sekeres?

DR. SEKERES: I have a question. I was interested by the data that were presented about breast cancer-specific mortality.

Does the FDA have any sense of whether

disease-specific mortality, in general, on clinical trials are accurate and whether that relatively accuracy varies by whether or not you have blinding in this study?

DR. KEEGAN: I'll let Dr. Pai-Scherf answer as a reviewer who is looking more at the primary data. I think we tend not to focus so much on cause-specific mortality for -- cancer-specific mortality unless it was a prespecified endpoint of the trial, and we're really more focused on understanding what are the clinical consequences of the toxicity, which is why we conduct this very careful review of the deaths, to determine what's the ultimate severity, the irreversible outcome that could occur, how severe is this and what are the risks.

So it's really more looking at it not from can we count which death is disease-related or not, but making a risk assessment, we need to know which deaths we think are really directly attributable to having gotten the drug.

DR. SEKERES: So I'm guessing the FDA has

not had a chance to validate the breast cancer-specific mortalities that were presented.

DR. PAI-SCHERF: Not for all cases. The vast majority were reported as deaths due to progressive disease. It is possible that X percentage of these patients might have suffered toxicities due to treatment progressed, but the treatment could have hastened the death. We have no way of knowing that other than reviewing individual cases, individual patient reports.

DR. SEKERES: Thank you.

DR. MIDTHUN: Dr. Curt?

DR. CURT: As I recall, the individual components of the AVADO and RIBBON trials were powered to independent analysis. And within RIBBON, we do have this one bit of evidence in the capecitabine arm, with more than 600 patients and the three-month improvement in overall survival for that particular arm. And I'm wondering how the agency looks at that information as the evidence for clinical activity that you were seeking within this suite of studies.

DR. KEEGAN: What we were really looking at -- although I think we're comparing one positive study, what we really want to do is get the sense of what is the totality, what's the consistent finding across studies, and that looks a little bit to the high end, the AVADO things look a little bit to the low end.

We think truth is somewhere in and around there, but I don't think we wanted to rely just on this one cohort, although it was independently powered, but to look across the totality of the data.

DR. MIDTHUN: I think Dr. Freedman, and then Dr. Wilson.

DR. FREEDMAN: The point that's often made is that crossover confounds studies, but, in fact, in the E2100, I don't believe that patients were allowed to receive Avastin. So that's, I think, an important issue.

The other thing is I was wondering whether FDA looked at whether the hazard ratio was affected by not censoring patients when they continued on

Avastin; in other words, those patients that stopped the paclitaxel because of toxicity or whatever reason, but continued on Avastin.

Did they compare the hazard ratios for that study by censoring it, censoring at that point?

DR. ROTHMANN: We didn't do any analysis comparing subjects who sort of crossed over and continued Avastin with those who did not. We didn't do any such analysis.

DR. WILSON: I have a question about the super responders. However, I did want to just comment on Dr. Curt's comment about the capecitabine-Avastin arm.

I think if one looks at this, much of the delta is being driven by the fact that the control arm is low, not that the treatment arm is high, which gets at a little bit of what I was referring to before.

We've heard today, and we've heard it both from patients and we've heard it from treating doctors, as well, that they have seen what seems to be termed super responders to this drug, to these

drug combinations. And I think that it was commented here that it's impossible to separate out the contribution of the Avastin from the chemotherapy simply because they're being given together.

I will say that having been one of the original developers of Taxol back in the early 1990s, I saw numerous patients go on for numbers of years on single-agent drug.

However, having said that, I'm just wondering, in looking, for example, at the AVADO trial and looking at these progression-free survival curves, I see no evidence of any difference beyond 18-24 months where these super responders would be, because to be a super responder, you would be responding for an excess period of time.

So I was just wondering what CDER's thought is about this, because we're hearing this, and I don't see it in these curves. I see something in the E2100, but I think we all are questioning whether or not this is being driven by an outlier

curve, i.e., the control arm being abnormally low.

DR. KEEGAN: I think the best we can say about the super responders is that if you look at the controlled clinical trials, we're not seeing a group that looks like this. And in addition to separating out the underlying treatment, there's also just the patient's natural history of the disease, and there's an enormous variety of how patients who were diagnosed with first-line metastatic breast cancer are going to do.

It's not like other diseases with very short and very predictable courses. This is very different. So in the absence of a clinical trial and a control, I think we're having a hard time identifying those patients, and from the survival curves, from the progression-free survival curves, we're just not seeing that population. And I think the most compelling thing is that 2400 patients, I mean, in 2,400 patients, there doesn't seem to be a group emerging that's behaving differently.

DR. WILSON: So I guess that's kind of my read, too, and I just think it's very important to

recognize that these agents alone can result in extremely long durations of response, and simply having a good outcome with the combination in no way means that you wouldn't have had a similarly good outcome with the chemotherapy alone.

It happens and it looks in these curves to be happening at the same frequency, and I think that's very important for patients with breast cancer, because if they're being told by their doctors that their excellent outcome is being driven by this combination rather than by the chemotherapy drug, I'm not sure that they're being well served. And I think that the only way that we can even address that is through looking at these clinical trials, because as we've already said, these drugs are not given -- the Avastin is not given alone.

DR. MIDTHUN: I have a question just to make sure I understand correctly, and I think this follows-up on something that Dr. Portis asked.

So when you are talking about the deaths that occurred that you thought were attributable to

Avastin, I think you were saying in those slides that you showed that there wasn't a significant difference in the percentage of adverse events on study that resulted in death, but when you looked at some of them, they were very much characteristic of what you would expect to be an adverse outcome of Avastin.

I just want to make sure I understand that.

DR. PAI-SCHERF: That's correct, Dr. Midthun. That's correct.

DR. MIDTHUN: Then I had one other question. In looking at the way some of these studies are planned, it really appears that the statistical plan and the powering of the study really is based on a particular hazard ratio that you might want to be able to demonstrate.

I noted that in some of the materials, it was indicated that a number of these studies were set up to be able to demonstrate a hazard ratio in the vicinity of .7 to .75. And I was just wondering if that was sort of a fairly routine way of approaching these kinds of studies.

DR. SRIDHARA: Yes. At the beginning of the study or before the start of the study, when they are planning, they do size the study based on a hazard ratio, assuming the control arm effect size in some way, and coming up with what is a clinically meaningful effect.

So based on that, it is planned. But not all the times do we get to see the protocol before it is started to comment on whether the effect that they are sizing is clinically meaningful or not.

DR. KEEGAN: I just want to clarify that I think the statisticians are very comfortable looking at the hazard ratios, but speaking from the clinical point of view, we always ask for the background assumptions, what are they looking for, what do they expect in the control arm, what difference are they sizing the trial for, because I, speaking for myself, don't think in hazard ratios. It sounds like it's in the ballpark, but we always ask for those underlying assumptions so that we really have a better understanding and don't consider the hazard ratio in isolation.

DR. MIDTHUN: I guess one thing that was interesting in looking at the data was that you had, in some cases, hazard ratios that were lower, but differences in median progression-free survival that were quite small. In other cases, the hazard ratio was higher, but there was a higher delta in the median. So it, obviously, can be a challenge.

Are there other questions from the advisory committee members?

[No response.]

DR. MIDTHUN: I do have one last question. Clearly, these are really difficult assessments in terms of trying to understand the risks and the benefits and weigh them against each other, and I think what I've heard today is that had you seen, as you said, I think, one other positive trial, something where the magnitude of the impact on progression-free survival was comparable to what you had seen in E2100, that was what you were looking for. And I recognize that it's very hard to put any kind of a specific time on that, but could you maybe talk about it a little bit more?

What you saw in E2100 was 5.5 months. So was it something sort of in that vicinity?

Could you address that?

DR. KEEGAN: I think based on the discussions at the December 5th, 2007 ODAC, the sense of the committee was that -- I mean, there were clearly some individuals who felt that PFS was not good enough and that there wasn't enough, but there were others who felt that that magnitude might itself constitute.

So I think we were influenced by that advice in terms of thinking this might be in the ballpark, but I would say -- and as you can see from the committee's vote, that was not necessarily a unanimous opinion on the magnitude and how beneficial it was. But there were certainly a number of people who felt that it was about the right size.

DR. PAZDUR: Then, obviously, as we've said, nobody is arguing whether an effect occurs. The robustness was never an issue. But because of the numerous issues that we had with the trial,

including one trial, a fail trial, the missing data, people not going to the prespecified endpoint, missing scans, et cetera, we really felt that there needed to be confirmation for the determination of the magnitude of benefit if we were going to be resting an approval on this 5.5 months, or if you even want to term it in the hazard ratio, it didn't really matter to me, but the similar effect.

That's what was kind of really discussed at the meeting. If you really read the minutes of that meeting, magnitude, magnitude, magnitude was the thing that was coming up of why we should approve the drug from their own consultants, and our presentations were primarily we're not sure of this magnitude, we're not sure of this magnitude. So that was the dilemma.

DR. MIDTHUN: Thank you. Are there other questions from the advisory committee members?

[No response.]

DR. MIDTHUN: If not, I am going to close this session, and then there will be a 15-minute

break before the last clarifying question session.

Thank you. So now it is, let's say, 5 past 3:00. So we'll start at 3:20.

(Whereupon, a recess was taken.)

Clarifying Questions of CDER Witnesses by CDER

DR. MIDTHUN: We will begin the clarifying questions for today's session, which is a 15-minute session in which CDER gets to ask clarifying questions of its presenters, and so we will now begin.

MS. CARTWRIGHT: Thank you, and good afternoon. We just have a few clarifying questions.

Dr. Keegan, when you were discussing the capecitabine arm of RIBBON-1, can you clarify what you meant about the amount of PFS at 2.9 months, please?

DR. KEEGAN: I think my response was that the 2.9-month difference in PFS was a statistically significant difference for the capecitabine arm, but the 2.9-month difference in overall survival was not a statistically significant difference.

MS. CARTWRIGHT: Thank you.

Dr. Pazdur, just to clarify, are you saying that if another study was conducted that showed either the same hazard ratio or the same amount of progression-free survival seen in the E2100 trial, that would be enough to confirm the magnitude?

DR. PAZDUR: We wanted to see both PFS and hazard ratio verify the magnitude of E2100. So it's "and" and not "or."

MS. CARTWRIGHT: There was also some discussion about the indication for Avastin progressed cancer.

Dr. Keegan, can you clarify for us what other treatment options are available that are less limited than the Avastin indication?

DR. KEEGAN: So I'm going to bring up slide 99 first and then 100. So this is a listing of FDA-approved drugs that are currently available for treatment of patients with metastatic breast cancer that are unrestricted based on HER2 positivity and would be considered available therapy in this population.

In addition, if you go to slide 100, many of the patients in the trial were ER and/or PR positive, and these additional therapies are also FDA-approved and available therapy for this population.

MS. CARTWRIGHT: Thank you. That's all we have.

Adjournment

DR. MIDTHUN: All right. Thank you very much. I thank everyone for their participation at the hearing today, and we will come back tomorrow morning and start punctually at 8:00 a.m. Thank you.

(Whereupon, at 3:23 p.m., the meeting was concluded.)